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234 240 246 253 254 25Y
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313 31Y 323 32Y 338 351
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367 368 36Y 37X 387
389 395 39Y 490 491 502
50Y 605 60Y 620 623 624
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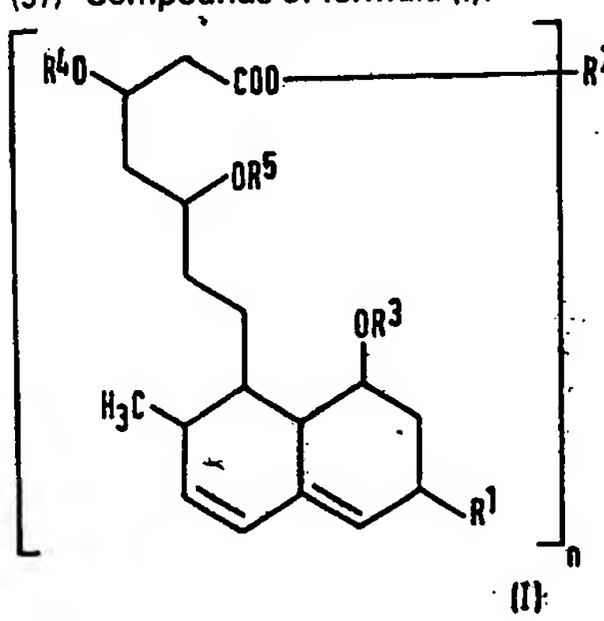
(54) Compounds Which Inhibit Cholesterol Biosynthesis, and Their Preparation

(57) Compounds of formula (I):



(I)

(wherein R^1 represents a hydrogen atom or a methyl group; R^2 represents a hydrogen atom, the alcoholic moiety of an ester or the cationic moiety of a salt; R^3, R^4 and R^5 are the same or different and each represents a hydrogen atom or an organic or inorganic acyl group, provided that, when R^3 represents a 2-methylbutyryl group, R^4 and R^5 both represent acyl groups; and *n* is the valency of R^2) may be prepared by cultivating microorganisms of the genera *Penicillium* or *Monascus* or by salifying or esterifying the corresponding carboxylic acid or lactone or, in the case of esters of the above formula (I), by esterifying a corresponding salt of the above formula (I).

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FIG. 1

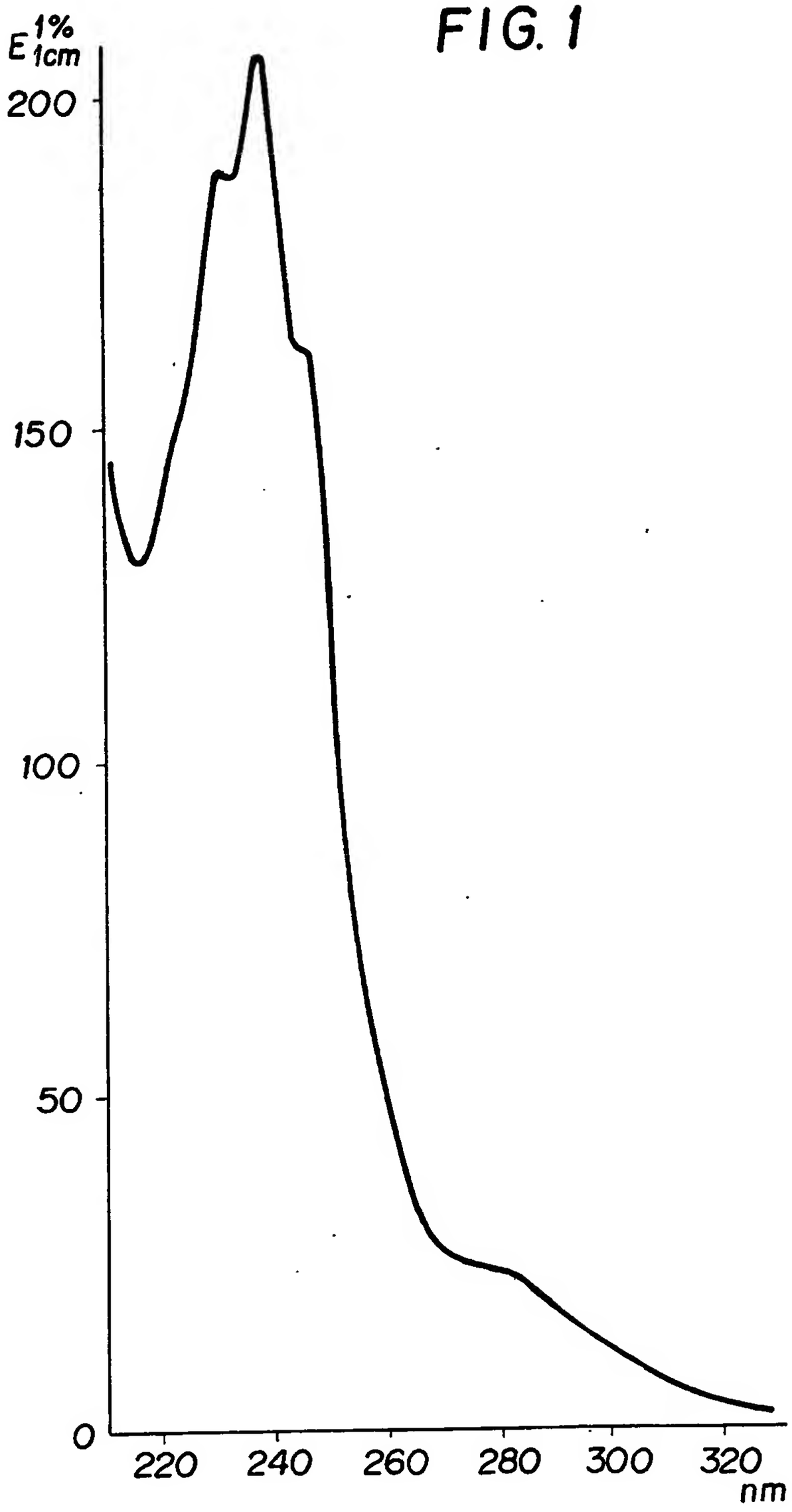

FIG. 2

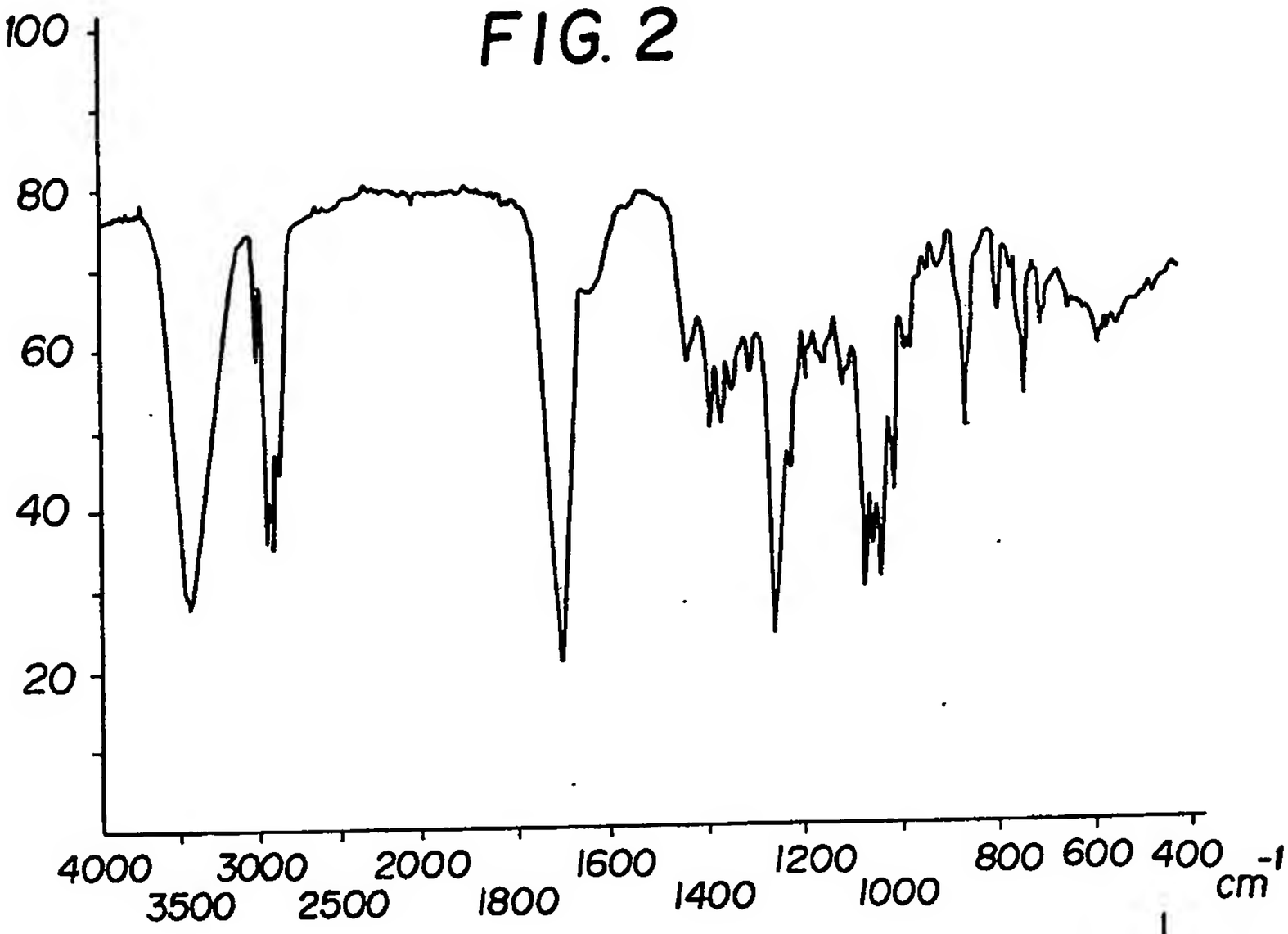
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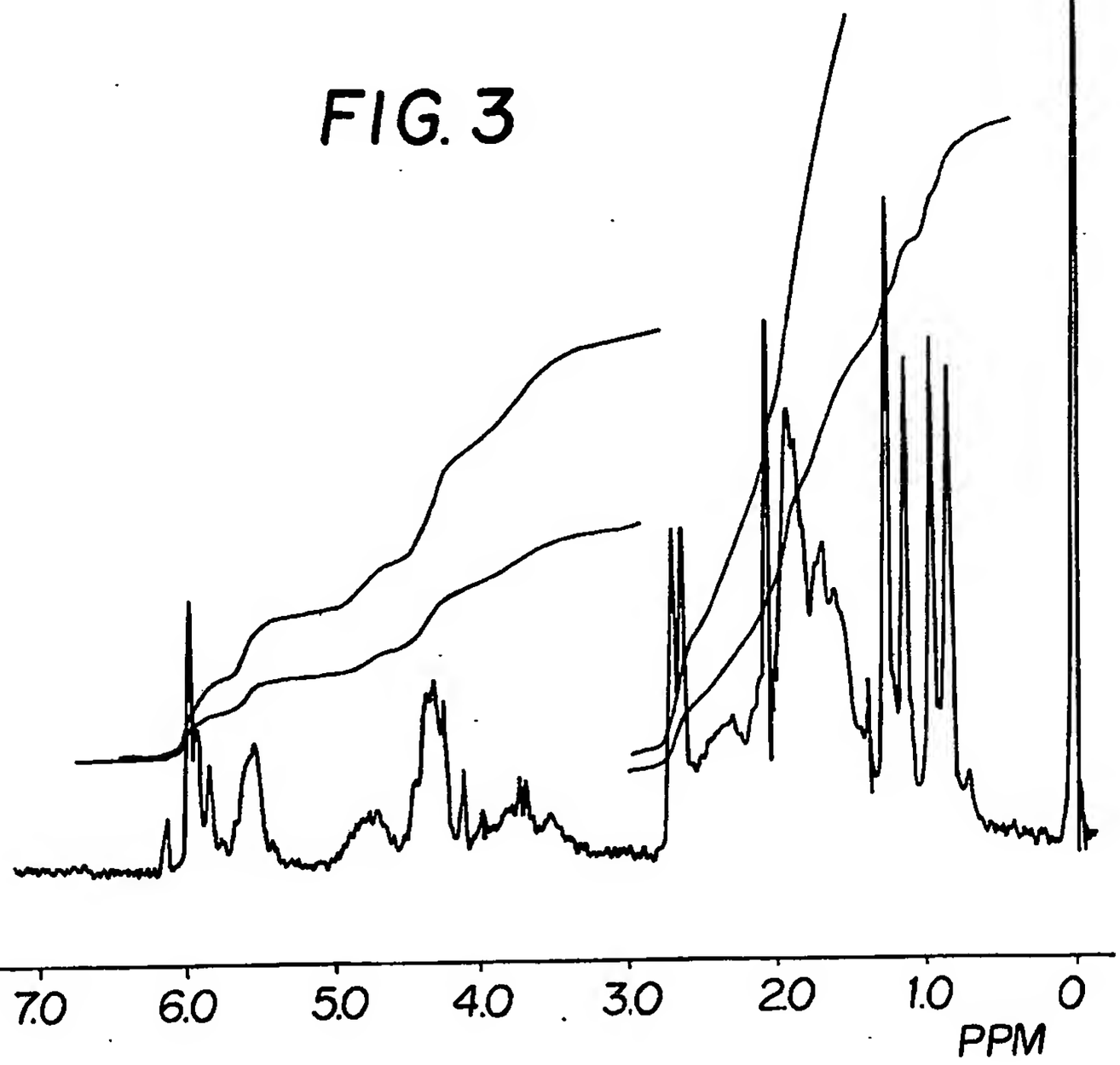
FIG. 3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SPECIFICATION

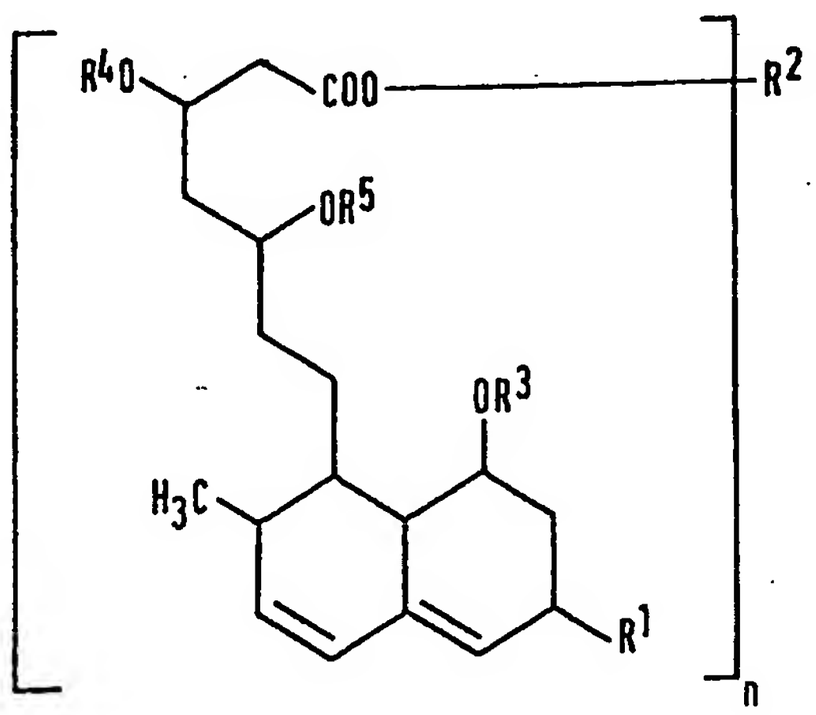
Compounds Which Inhibit Cholesterol Biosynthesis, and Their Preparation

The present invention relates to a series of novel compounds which have been found to inhibit cholesterol biosynthesis and which can thus be used in the treatment and prevention of disorders arising from high levels of cholesterol in the body. The invention also provides processes for preparing these compounds.

Hyperlipaemia, especially hypercholesteraemia, is known to be one of the main causes of cardiopathy, such as cardiac infarction or arteriosclerosis. As a result, considerable research has been carried out in an effort to discover compounds capable of reducing lipid, and especially cholesterol, levels in the blood. A group of compounds of this type is disclosed in US Patent Specification No. 3,983,140 and was isolated from microorganisms of the genus *Penicillium;* this group of compounds is collectively designated ML-236. Also, United Kingdom Patent Applications No. 2046737 and No. 2049664 disclose a structurally similar compound designated Monacolin K or MB-530B, and certain salts and esters of MB-530B are disclosed in United Kingdom Patent Application No. 2055100. MB-530B and its salts may be prepared by cultivating microorganisms of the genus *Monascus,* especially, but not exclusively, strains of *Monascus ruber.* Another compound of the MB-530 group, designated MB-530A, as well as other compounds related to the ML-236 and MB-530 groups are disclosed in our co-pending United Kingdom Patent Application No. 8110075.

We have now discovered a series of compounds related to the ML-236 and MB-530 groups which also have valuable inhibitory activity against the biosynthesis of cholesterol.

The compounds of the invention have the formula (I):



(I)

wherein:

R^1 represents a hydrogen atom or a methyl group;

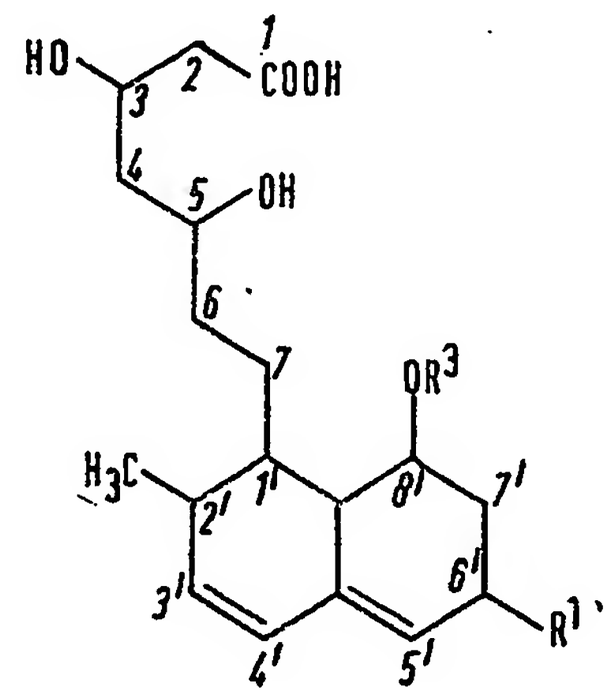
R^2 represents a hydrogen atom, the alcoholic moiety of an ester or the cationic moiety of a salt;

R^3, R^4 and R^5 are the same or different and each represents a hydrogen atom or an organic or inorganic acyl group, provided that, when R^3 represents a 2-methylbutyryl group, R^4 and R^5 both represent acyl groups; and

n is the valency of R^2.

The invention also provides processes for preparing the compounds of the invention by fermentation employing microorganisms of the genus *Penicillium* or *Monascus* or by hydrolysis, salification or esterification reactions commencing with such fermentation products.

As the compounds of the invention are derivatives of the ML-236 and MB-530 group compounds in which the lactone ring has been broken, they are named as derivatives of ML-236 carboxylic acids or MB-530 carboxylic acids (i.e. the carboxylic acids obtained by hydrolysis of ML-236 or MB-530 compounds) and the numbering system is that shown on the following structure:



(in which R^1 and R^3 are as defined above).

In the compounds of formula (I), where R^2 represents the cationic moiety of a salt, it may be a metal atom, for example an alkali metal atom (e.g. sodium or potassium), an alkaline earth metal atom (e.g. calcium, magnesium or barium), a transition metal atom (e.g. iron, nickel or cobalt) or other metal atoms (e.g. aluminium, zinc or copper); in this case, *n* will be the well-known valency of these metals, in the examples given normally varying from 1 to 3. Alternatively, it may be an ammonium group or a substituted ammonium group (preferably an alkyl-substituted ammonium group), such as methylammonium, ethylammonium, isopropylammonium, dimethylammonium, diethylammonium, trimethylammonium, triethylammonium, tetramethylammonium, or dicyclohexylammonium; in this case, *n* will be 1. Another cationic moiety which may be represented by R^2 is the salt-forming group derived from a basic amino acid, such as lysine, arginine or ornithine.

Alternatively, R^2 may be the alcoholic moiety of an ester, in which case the value of *n* will depend upon the nature of the hydroxy compound from which R^2 is derived; for example in the case of mono-alcohols, *n* would be 1, in the case of glycols, *n* would be 2 and in the case of glycerol, *n* would be 3. Where R^2 represents a monovalent group, this is preferably an unsubstituted or substituted alkyl group, an unsubstituted or substituted aralkyl group or an unsubstituted or substituted phenacyl group.

Examples of alkyl groups which may be represented by R^2 include straight and branched chain alkyl groups, preferably having from 1 to 8 carbon atoms, for example the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, sec-pentyl, t-pentyl, isopentyl, neopentyl, hexyl, heptyl, 2-methylhexyl and octyl groups.

Examples of aralkyl groups which may be represented by R^2 include the benzyl group and the benzhydryl group, both of which may be unsubstituted or have one or more substituents in the benzene ring. Examples of such substituents include: C_1—C_4 alkyl groups (methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or t-butyl), C_1—C_4 alkoxy groups (methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy or t-butoxy), halogen atoms (e.g. chlorine, bromine or fluorine) or the trifluoromethyl group. Where there are two or more substituents, these may be the same or different. Examples of such aralkyl groups include the benzyl, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-ethylbenzyl, 3-ethylbenzyl, 4-ethylbenzyl, 2-propylbenzyl, 3-propylbenzyl, 4-propylbenzyl, 2-butylbenzyl, 3-butylbenzyl, 4-butylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 2-propoxybenzyl, 3-propoxybenzyl, 4-propoxybenzyl, 4-butoxybenzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl and benzhydryl groups.

Where R^2 represents a phenacyl group, this may be unsubstituted or may have one or more substituents in the benzene ring. Examples of such substituents include: C_1—C_4 alkyl groups, C_1—C_4 alkoxy groups, halogen atoms and the trifluoromethyl group; specific examples of these substituent groups are given above. Preferred examples of such phenacyl groups include the phenacyl, 2-methylphenacyl, 3-methylphenacyl, 4-methylphenacyl, 2-ethylphenacyl, 3-ethylphenacyl, 4-ethylphancyl, 2-propylphenacyl, 3-propylphenacyl, 4-propylphenacyl, 2-butylphenacyl, 3-butylphenacyl, 4-butylphenacyl, 2-methoxyphenacyl, 3-methoxyphenacyl, 4-methoxyphenacyl, 2-ethoxyphenacyl, 3-ethoxyphenacyl, 4-ethoxyphenacyl, 2-propoxyphenacyl, 3-propoxyphenacyl, 4-propoxyphenacyl, 2-butoxyphenacyl, 3-butoxyphenacyl, 4-butoxyphenacyl, 2-chlorophenacyl, 3-chlorophenacyl, 4-chlorophenacyl, 2-bromophenacyl, 3-bromophenacyl, 4-bromophenacyl, 2-fluorophenacyl, 3-fluorophenacyl, 4-fluorophenacyl, 2-trifluoromethylphenacyl, 3-trifluoromethylphenacyl, and 4-trifluoromethylphenacyl groups.

Where R^2 represents a bivalent alcoholic moiety, it is preferably a C_2—C_6 alkylene or alkylidene group, for example an ethylene, ethylidene, propylene, propylidene, trimethylene, tetramethylene,

butylidene, pentamethylene or pentylidene group, as well as such groups having one or more substituents, e.g. hydroxy groups, halogen atoms or trifluoromethyl groups.

Where R^2 represents a trivalent alcoholic moiety, it is preferably a saturated aliphatic hydrocarbon group having from 2 to 6 carbon atoms and optionally one or more substituents, e.g. hydroxy groups, halogen atoms or trifluoromethyl groups.

Where R^3, R^4 or R^5 represents an acyl group, this may be an organic acyl group (for example an aliphatic acyl group, an aromatic acyl group, an araliphatic acyl group, an alicyclic acyl group, a heterocyclic acyl group, a heterocyclic-substituted aliphatic acyl group, an aliphatic sulphonyl group, an aromatic sulphonyl group, an aliphatic phosphoryl group, an aromatic phosphoryl group or an araliphatic phosphoryl group) or an inorganic acyl group (for example an acyl group derived from phosphoric acid, sulphuric acid or nitric acid).

Where the acyl group is an aliphatic acyl group, this may be saturated or unsaturated and examples include: straight or branched chain C_2—C_{20} alkanoyl groups (e.g. the acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, 2-methylvaleryl, heptanoyl, isoheptanoyl, octanoyl, isooctanoyl, 2-methyloctanoyl, nonanoyl, isononanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, palmitoyl, stearoyl, isostearoyl, nonadecanoyl and eicosanoyl groups); C_3—C_{20} alkenoyl groups (e.g. the acryloyl, crotonoyl, 3-butenoyl, methacryloyl, 3-methyl-2-butenoyl, 2-pentenoyl, 4-pentenoyl, tigloyl, angeloyl, 2-hexenoyl, 2-heptenoyl, hepta-2,4-dienoyl, 2-octenoyl, 2-nonenoyl, 2-decenoyl, 2-undecenoyl, linolenoyl, oleoyl, linoleoyl and arachidonoyl groups); and C_3—C_{20} alkynoyl groups (e.g. the propioloyl, 2-butynoyl. 3-butynoyl, 2-pentynoyl, 2-hexynoyl, 2-heptynoyl, 2-octynoyl, 2-nonynoyl and 2-decynoyl groups). These acyl groups may be unsubstituted or may have one or more substituents, for example: halogen atoms, such as chlorine or bromine; the trifluoromethyl group; the nitro group; the carboxy group; alkoxycarbonyl groups, such as methoxycarbonyl or ethoxycarbonyl; aralkoxycarbonyl groups, such as benzyloxycarbonyl; the cyano group; the amino group; alkanoylamino groups; such as acetylamino; alkylamino groups, such as methylamino, dimethylamino or ethylamino; aralkylamino groups, such as benzylamino; the hydroxy group; alkanoyloxy groups, such as acetoxy or pivaloyloxy; alkoxy groups, such as methoxy or ethoxy; the sulphhydryl group; alkylthio groups, such as methylthio or ethylthio; and acylthio groups, such as acetylthio or benzylthio.

Where the acyl group represented by R^3, R^4 or R^5 is an aromatic acyl group, the aromatic ring may be a single ring (e.g. a benzene ring) or a fused ring, for example a naphthalene ring, an anthracene ring or an indan ring. This ring may optionally have one or more substituents, for example alkyl groups, alkoxy groups, halogen atoms, trifluoromethyl groups, nitro groups, cyano groups, amino groups or hydroxy groups; where there are two or more substituents, these may be the same or different. Specific examples of such aromatic acyl groups include the benzoyl, *o*-toluoyl, *m*-toluoyl, *p*-toluoyl, 2,4-dimethylbenzoyl, 3,4-dimethylbenzoyl, 2-ethylbenzoyl, 3-ethylbenzoyl, 4-ethylbenzoyl, 2-propylbenzoyl, 3-propylbenzoyl, 4-propylbenzoyl, 4-butylbenzoyl, *o*-anisoyl, *m*-anisoyl, *p*-anisoyl, 2,4-dimethoxybenzoyl, 2-ethoxybenzoyl, 3-ethoxybenzoyl, 4-ethoxybenzoyl, 2-propoxybenzoyl, 3-propoxybenzoyl, 4-propoxybenzoyl, 2-butoxybenzoyl, 3-butoxy benzoyl, 4-butoxybenzoyl, piperonyloyl, 2-chlorobenzoyl, 3-chlorobenzoyl, 4-chlorobenzoyl, 2,3-dichlorobenzoyl, 3,4-dichlorobenzoyl, 2,4-dichlorobenzoyl, 2-bromobenzoyl, 3-bromobenzoyl, 4-bromobenzoyl, 2-fluorobenzoyl, 3-fluorobenzoyl, 4-fluorobenzoyl, 2-trifluoromethylbenzoyl, 3-trifluoromethylbenzoyl, 4-trifluoromethylbenzoyl, 2-nitrobenzoyl, 3-nitrobenzoyl, 4-nitrobenzoyl, 2,4-dinitrobenzoyl, 3,5-dinitrobenzoyl, salicyloyl, 3-hydroxybenzoyl, 4-hydroxybenzoyl, 2-acetoxybenzoyl, 3-acetoxybenzoyl, 4-acetoxybenzoyl, anthraniloyl, 2-acetamidobenzoyl, 4-acetamidobenzoyl, vanilloyl, veratroyl, protocatechuoyl, galloyl, 1-naphthoyl, 2-naphthoyl, 2-anthranoyl, 4-indanecarbonyl, 5-indanecarbonyl and 4-indenecarbonyl groups.

Where the acyl group represented by R^3, R^4 or R^5 is an araliphatic acyl group, the aromatic ring in this araliphatic acyl group may be a single ring or a fused ring, as exemplified above for the aromatic acyl group, whilst the aliphatic moiety may be saturated or unsaturated. The aromatic ring may optionally have one or more substituents, as exemplified above for the aromatic acyl groups. Examples of such araliphatic acyl groups include the phenylacetyl, 2-methylphenylacetyl, 3-methylphenylacetyl, 4-methylphenylacetyl, 2-ethylphenylacetyl, 2-methoxyphenylacetyl, 3-methoxyphenylacetyl, 4-methoxyphenylacetyl, 2-ethoxyphenylacetyl, 3-ethoxyphenylacetyl, 4-ethoxyphenylacetyl, 2-propoxyphenylacetyl, 3-propoxyphenylacetyl, 4-propoxyphenylacetyl, 2,4-dimethoxyphenylacetyl, 3,4-methylenedioxyphenylacetyl, 2-hydroxyphenylacetyl, 3-hydroxyphenylacetyl, 4-hydroxyphenylacetyl, 2-chlorophenylacetyl, 3-chlorophenylacetyl, 4-chlorophenylacetyl, 2,3-dichlorophenylacetyl, 2,4-dichlorophenylacetyl, 3,5-dichlorophenylacetyl, 2-bromophenylacetyl, 3-bromophenylacetyl, 4-bromophenylacetyl, 2-nitrophenylacetyl, 3-nitrophenylacetyl, 4-nitrophenylacetyl, 4-aminophenylacetyl, 2-phenylpropionyl, 3-(2-methylphenyl)propionyl, 3-(3-methylphenyl)propionyl, 3-(4-methylphenyl)propionyl, 3-(2-methoxyphenyl)propionyl, 3-(3-methoxyphenyl)propionyl, 3-(4-methoxyphenyl)propionyl, 3-(3,4-methylenedioxyphenyl)propionyl, 3-(2-chlorophenyl)propionyl, 3-(3-chlorophenyl)propionyl, 3-(4-chlorophenyl)propionyl, phenoxyacetyl, cinnamoyl, *o*-methylcinnamoyl, *m*-methylcinnamoyl, *p*-methylcinnamoyl, *o*-methoxycinnamoyl, *m*-methoxycinnamoyl, *p*-methoxycinnamoyl, *o*-hydroxycinnamoyl, *m*-hydroxycinnamoyl, *p*-hydroxycinnamoyl, *o*-

chlorocinnamoyl, *m*-chlorocinnamoyl, *p*-chlorocinnamoyl, *o*-bromocinnamoyl, *m*-bromocinnamoyl and *p*-bromocinnamoyl groups.

Where the acyl group represented by R^3, R^4, or R^5 is an alicyclic acyl group, the alicyclic ring may be saturated or unsaturated and preferably has from 3 to 7 carbon atoms. Examples of such alicyclic acyl groups include the cyclopropanecarbonyl, cyclobutanecarbonyl, cyclobut-1-enecarbonyl, cyclobut-2-enecarbonyl, cyclo-pentanecarbonyl, cyclopent-1-enecarbonyl, cyclopent-2-enecarbonyl, cyclopenta-1,3-dienecarbonyl, cyclopenta-2,4-dienecarbonyl, cyclohexanecarbonyl, cyclohex-1-enecarbonyl, cyclohex-2-enecarbonyl, cyclohex-3-enecarbonyl, cyclohexa-1,3-dienecarbonyl, cyclohexa-2,4-dienecarbonyl, cycloheptanecarbonyl, cyclohept-1-enecarbonyl, cyclohept-2-enecarbonyl, cyclohept-3-enecarbonyl, cyclohepta-1,3-dienecarbonyl, cyclohepta-2,4-dienecarbonyl, cyclohepta-2,5-dienecarbonyl, cyclohepta-1,4-dienecarbonyl, cyclohepta-1,5-dienecarbonyl, cyclohepta-1,3,5-trienecarbonyl, cyclohepta-2,4,6-trienecarbonyl and adamantanecarbonyl groups. These rings may optionally have one or more substituents, as exemplified above in respect of the aromatic acyl groups and such substituents may form one or more rings fused to the abovementioned alicyclic ring system.

Where the acyl group represented by R^3, R^4 or R^5 is a heterocyclic acyl group, the heterocyclic ring preferably has 5 or 6 ring atoms, one or more of which is a hetero atom, for example a nitrogen atom, an oxygen atom, a sulphur atom or a selenium atom. This heterocyclic ring may optionally be fused with a carbocyclic ring or with another heterocyclic ring (which may be the same as or different from the first-mentioned heterocyclic ring) to form a fused heterocyclic ring system. The heterocyclic acyl group may have one or more substituents, as exemplified above in respect of the aromatic acyl groups. Specific examples of such heterocyclic acyl groups include the 2-thenoyl, 3-thenoyl, 5-methylthen-2-oyl, 5-chlorothen-2-oyl, 4,5-dimethylthen-3-oyl, 2-furoyl, 3-furoyl, 5-methylfur-2-oyl, 5-chlorofur-2-oyl, pyridine-2-carbonyl, 3-methylpyridine-2-carbonyl, 4-methylpyridine-2-carbonyl, 5-methylpyridine-2-carbonyl, 6-methyl-pyridine-2-carbonyl, nicotinoyl, isonicotinoyl, isoxazole-3-carbonyl, isoxazole-4-carbonyl, oxazole-2-carbonyl, oxazole-4-carbonyl, 4-acetylaminothiazole-2-carbonyl, 1,3,4-thiadiazole-2-carbonyl, 5-methyl-1,3,4-thiadiazole-2-carbonyl, 1,2,3-triazole-1-carbonyl, 1,2,3,4-tetrazole-1-carbonyl, piperidinecarbonyl, 4-methyl-1-piperazine-carbonyl, 1-pyrrolidinecarbonyl, benzofuran-2-carbonyl and benzothiophene-2-carbonyl groups.

Where the acyl group represented by R^3, R^4 or R^5 is a heterocyclic- substituted aliphatic acyl group, the heterocyclic group may be as described above for the heterocyclic acyl groups and the aliphatic moiety may be saturated or unsaturated and may be as described above for aliphatic acyl groups. Examples of such heterocyclic-substituted aliphatic acyl groups include the 2-thienylacetyl, (5-methylthiophene-2-yl)acetyl, (5-chlorothiophene-2-yl)acetyl, 3-thienylacetyl, 2-furylacetyl, 3-furylacetyl, 2-pyridylacetyl, 3-pyridylacetyl, 4-pyridylacetyl, 2-furylacryloyl, 3-furylacryloyl, 2-thienylacryloyl, 3-thienylacryloyl, piperidinoacetyl and 4-methylpiperidinoacetyl, 2-amino-3-(indol-2-yl)propionyl and 2-amino-3-(indol-3-yl)propionyl groups.

Where the acyl group represented by R^3, R^4 or R^5 is a sulphonyl group, this may be an aliphatic sulphonyl group (for example a methanesulphonyl or ethanesulphonyl group) or an aromatic sulphonyl group (e.g. a benzene-sulphonyl or toluenesulphonyl group).

Where the acyl group represented by R^3, R^4 or R^5 is a phosphoryl group, this may be an aliphatic phosphoryl group (e.g. a dimethylphosphoryl or diethylphosphoryl group), an aromatic phosphoryl group (e.g. a ditolylphosphoryl group) or an araliphatic phosphoryl group (e.g. a dibenzylphosphoryl, *p*-methylbenzylphosphoryl, *p*-bromobenzylphosphoryl or *p*-methoxybenzylphosphoryl group).

Of the compounds of the invention, those compounds are preferred where:

R^1 represents a hydrogen atom or a methyl group;

R^2 represents a hydrogen atom, a metal atom (particularly an alkali metal atom, an alkaline earth metal atom or an aluminium, zinc, iron or germanium atom), an ammonium group, an alkyl- substituted ammonium group, a group capable of forming a salt derived from a basic amino acid, an alkyl group (preferably a straight or branched chain C_1—C_8 alkyl group), an aralkyl group optionally having one or more substituents on the aryl moiety or a phenacyl group optionally having one or more substituents on the phenyl moiety, those substituents being selected from C_1—C_4 alkyl groups, C_1—C_4 alkoxy groups, halogen atoms and trifluoromethyl groups; and

R^3, R^4 and R^5 are the same or different and each represents a hydrogen atom, an aliphatic acyl group (preferably a C_2—C_{20} alkanoyl group, a C_3—C_{20} alkenoyl group or a C_3—C_{20} alkynoyl group), an aromatic acyl group (preferably a C_7—C_{15} group) or an araliphatic acyl group (preferably a C_8 or C_9 aralkanoyl group or a C_9 aralkenoyl group) provided that, when R^3 represents a 2-methylbutyryl group, R^4 and R^5 both represent acyl groups.

More preferred compounds of formula (I) are those in which:

R^1 represents a hydrogen atom or a methyl group;

R^2 represents a hydrogen atom, an alkali metal atom, an alkaline earth metal atom, an ammonium group, a group capable of forming a salt derived from a basic amino acid, a C_1—C_4 alkyl group, a benzyl group or a phenacyl group; and

R^3, R^4 and R^5 are the same or different and each represents a hydrogen atom, a C_2—C_6 alkanoyl group, a C_3—C_6 alkenoyl group or a benzoyl group, provided that, when R^3 represents a 2-methylbutyryl group, both R^4 and R^5 represent acyl groups.

The most preferred compounds are those in which:

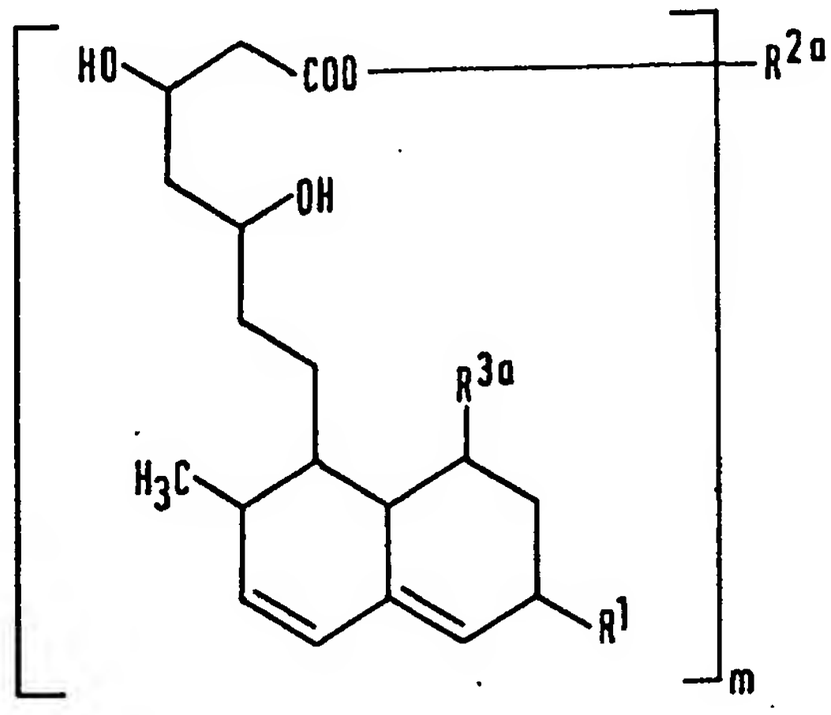
R^1 represents a hydrogen atom or a methyl group (particularly a hydrogen atom);

R^2 represents a C_1—C_4 alkyl group, a benzyl group or a phenacyl group (particularly a C_1—C_4 alkyl group);

R^3 represents a C_2—C_6 alkanoyl group or a C_3—C_6 alkenoyl group (particularly a C_2—C_6 alkanoyl group); and

R^4 and R^5 are the same or different and each represents a C_2—C_6 alkanoyl group or a benzoyl group (particularly an acetyl group or a benzoyl group).

One useful class of compounds of the present invention are those compounds of formula (II):



(II)

in which;

R^1 represents a hydrogen atom or a methyl group;

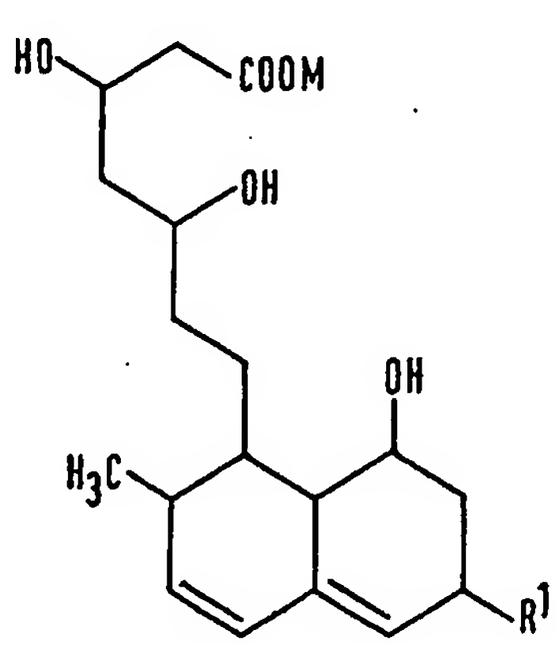
R^{2a} represents a hydrogen atom, an alkali metal atom, an alkaline earth metal atom, an ammonium group, a group capable of forming a salt derived from a basic amino acid, a C_1—C_4 alkyl group, a benzyl grou p or a phenacyl groupp

R^{3a} represents a C_2—C_6 alkanoyl group (other than a 2-methylbutyryl group) or a C_3—C_6 alkenoyl group; and

m is the valence of the atom or group represented by R^{2a}.

Particularly preferred are those compounds of formula (II) in which R^{2a} represents a C_1—C_4 alkyl group, a benzyl group or a phenacyl group and those compounds of formula (II) in which R^{2a} represents an alkali metal atom.

Another particularly useful class of compounds of the present invention are those compounds of formula (III):



(III)

in which:

R^1 represents a hydrogen atom or methyl group; and

M represents a hydrogen atom or an alkali metal atom, particularly an alkali metal atom and preferably a sodium atom.

Examples of compounds of the invention are given in the following list, in which, as explained above, the compounds are named as derivatives of ML-236A, ML-236B, MB-530A or MB-530B or their corresponding carboxylic acids:

1. Sodium ML-236A-carboxylate

2. Calcium bis(ML-236A-carboxylate)
3. Sodium MB-530A-carboxylate
4. Calcium bis(MB-530A-carboxylate)
5. Methyl ML-236A-carboxylate
6. Ethyl ML-236A-carboxylate
7. Butyl ML-236A-carboxylate
8. Benzyl ML-236A-carboxylate
9. *p*-Bromobenzyl ML-236A-carboxylate
10. *p*-Methoxybenzyl ML-236A-carboxylate
11. Phenacyl ML-236A-carboxylate
12. *p*-Methoxyphenacyl ML-236A-carboxylate
13. Methyl MB-530A-carboxylate
14. Ethyl MB-530A-carboxylate
15. Butyl MB-530A-carboxylate
16. Benzyl MB-530A-carboxylate
17. *p*-Methoxybenzyl-MB-530A-carboxylate
18. Phenacyl MB-530A-carboxylate
19. *p*-Methoxyphenacyl MB-530A-carboxylate
20. Sodium 8′-*O*-acetyl-ML-236A-carboxylate
21. Methyl 8′-*O*-acetyl-ML-236A-carboxylate
22. Ethyl 8′-*O*-acetyl-ML-236A-carboxylate
23. Butyl 8′-*O*-acetyl-ML-236A-carboxylate
24. Benzyl 8′-*O*-acetyl-ML-236A-carboxylate
25. *p*-Methoxybenzyl 8′-*O*-acetyl-ML-236A-carboxylate
26. Phenacyl 8′-*O*-acetyl-ML-236A-carboxylate
27. *p*-Methoxyphenacyl 8′-*O*-acetyl-ML-236A-carboxylate
28. Sodium 8′-*O*-acetyl-MB-530A-carboxylate
29. Methyl 8′-*O*-acetyl-MB-530A-carboxylate
30. Ethyl 8′-*O*-acetyl-MB-530A-carboxylate
31. Butyl 8′-*O*-acetyl-MB-530A-carboxylate
32. Benzyl 8′-*O*-acetyl-MB-530A-carboxylate
33. *p*-Methoxybenzyl 8′-*O*-acetyl-MB-530A-carboxylate
34. Phenacyl 8′-*O*-acetyl-MB-530A-carboxylate
35. *p*-Methoxyphenacyl 8′-*O*-acetyl-MB-530A-carboxylate
36. Sodium 8′-*O*-propionyl-ML-236A-carboxylate
37. Methyl 8′-*O*-propionyl-ML-236A-carboxylate
38. Ethyl 8′-*O*-propionyl-ML-236A-carboxylate
39. Benzyl 8′-*O*-propionyl-ML-236A-carboxylate
40. Phenacyl 8′-*O*-propionyl-ML-236A-carboxylate
41. Sodium 8′-*O*-propionyl-MB-530A-carboxylate
42. Methyl 8′-*O*-propionyl-MB-530A-carboxylate
43. Ethyl 8′-*O*-propionyl-MB-530A-carboxylate
44. Butyl 8′-*O*-propionyl-MB-530A-carboxylate
45. Benzyl 8′-*O*-propionyl-MB-530A-carboxylate
46. Phenacyl 8′-*O*-propionyl-MB-530A-carboxylate
47. Sodium 8′-*O*-butyryl-ML-236A-carboxylate
48. Magnesium bis(8′-*O*-butyryl-ML-236A-carboxylate)
49. Aluminium tris(8′-*O*-butyryl-ML-236A-carboxylate)
50. Methyl 8′-*O*-butryl-ML-236A-carboxylate
51. Ethyl 8′-*O*-butyryl-ML-236A-carboxylate
52. Butyl 8′-*O*-butyryl-ML-236A-carboxylate
53. Benzyl 8′-*O*-butyryl-ML-236A-carboxylate
54. Phenacyl 8′-*O*-butyryl-ML-236A-carboxylate
55. Dimethylaminoethyl 8′-*O*-butyryl-ML-236A-carboxylate
56. Sodium 8′-*O*-butyryl-MB-530A-carboxylate
57. Calcium bis(8′-*O*-butyryl-MB-530A-carboxylate)
58. Methyl 8′-*O*-butyryl-MB-530A-carboxylate
59. Ethyl 8′-*O*-butyryl-MB-530A-carboxylate
60. Butyl 8′-*O*-butyryl-MB-530A-carboxylate
61. Benzyl 8′-*O*-butyryl-MB-530A-carboxylate
62. Phenacyl 8′-*O*-butyryl-MB-530A-carboxylate
63. Sodium 8′-*O*-(4-pentenoyl)-ML-236A-carboxylate
64. Methyl 8′-*O*-(4-pentenoyl)-ML-236A-carboxylate
65. Ethyl 8′-*O*-(4-pentenoyl)-ML-236A-carboxylate
66. Butyl 8′-*O*-(4-pentenoyl)-ML-236A-carboxylate

67. Benzyl 8′-*O*-(4-pentenoyl)-ML-236A-carboxylate
68. Phenacyl 8′-*O*-(4-pentenoyl)-ML-236A-carboxylate
69. Sodium 8′-*O*-(4-pentenoyl)-MB-530A-carboxylate
70. Methyl 8′-*O*-(4-pentenoyl)-MB-530A-carboxylate
71. Ethyl 8′-*O*-(4-pentenoyl)-MB-530A-carboxylate
72. Butyl 8′-*O*-(4-pentenoyl)-MB-530A-carboxylate
73. Benzyl 8′-*O*-(4-pentenoyl)-MB-530A-carboxylate
74. Phenacyl 8′-*O*-(4-pentenoyl)-MB-530A-carboxylate
75. Sodium 8′-*O*-isovaleryl-ML-236A-carboxylate
76. Methyl 8′-*O*-isovaleryl-ML-236A-carboxylate
77. Ethyl 8′-*O*-isovaleryl-ML-236A-carboxylate
78. Butyl 8′-*O*-isovaleryl-ML-236A-carboxylate
79. Benzyl 8′-*O*-isovaleryl-ML-236A-carboxylate
80. Phenacyl 8′-*O*-isovaleryl-ML-236A-carboxylate
81. Sodium 8′-*O*-isovaleryl-MB-530A-carboxylate
82. Methyl 8′-*O*-isovaleryl-MB-530A-carboxylate
83. Ethyl 8′-*O*-isovaleryl-MB-530A-carboxylate
84. Butyl 8′-*O*-isovaleryl-MB-530A-carboxylate
85. Benzyl 8′-*O*-isovaleryl-MB-530A-carboxylate
86. Phenacyl 8′-*O*-isovaleryl-MB-530A-carboxylate
87. Sodium 8′-*O*-hexanoyl-ML-236A-carboxylate
88. Methyl 8′-*O*-hexanoyl-ML-236A-carboxylate
89. Ethyl 8′-*O*-hexanoyl-ML-236A-carboxylate
90. Butyl 8′-*O*-hexanoyl-ML-236A-carboxylate
91. Benzyl 8′-*O*-hexanoyl-ML-236A-carboxylate
92. Phenacyl 8′-*O*-hexanoyl-ML-236A-carboxylate
93. Sodium 8′-*O*-hexanoyl-MB-530A-carboxylate
94. Methyl 8′-*O*-hexanoyl-MB-530A-carboxylate
95. Ethyl 8′-*O*-hexanoyl-MB-530A-carboxylate
96. Butyl 8′-*O*-hexanoyl-MB-530A-carboxylate
97. Benzyl 8′-*O*-hexanoyl-MB-530A-carboxylate
98. Phenacyl 8′-*O*-hexanoyl-MB-530A-carboxylate
99. Sodium 8′-*O*-palmitoyl-ML-236A-carboxylate
100. Methyl 8′-*O*-palmitoyl-ML-236A-carboxylate
101. Benzyl 8′-*O*-palmitoyl-ML-236A-carboxylate
102. Phenacyl 8′-*O*-palmitoyl-ML-236A-carboxylate
103. Sodium 8′-*O*-palmitoyl-MB-530A-carboxylate
104. Methyl 8′-*O*-palmitoyl-MB-530A-carboxylate
105. Ethyl 8′-*O*-palmitoyl-MB-530A-carboxylate
106. Benzyl 8′-*O*-palmitoyl-MB-530A-carboxylate
107. Sodium 8′-*O*-stearoyl-ML-236A-carboxylate
108. Sodium 8′-*O*-stearoyl-MB-530A-carboxylate
109. Sodium 8′-*O*-linolenoyl-ML-236A-carboxylate
110. Methyl 8′-*O*-linolenoyl-ML-236A-carboxylate
111. Sodium 8′-*O*-linolenoyl-MB-530A-carboxylate
112. Methyl 8′-*O*-linolenoyl-MB-530A-carboxylate
113. Sodium 8′-*O*-benzoyl-ML-236A-carboxylate
114. Potassium 8′-*O*-benzoyl-ML-236A-carboxylate
115. Aluminium tris(8′-*O*-benzoyl-ML-236A-carboxylate)
116. Methyl 8′-*O*-benzoyl-ML-236A-carboxylate
117. Ethyl 8′-*O*-benzoyl-ML-236A-carboxylate
118. Butyl 8′-*O*-benzoyl-ML-236A-carboxylate
119. Benzyl 8′-*O*-benzoyl-ML-236A-carboxylate
120. *p*-Methoxybenzyl 8′-*O*-benzoyl-ML-236A-carboxylate
121. Phenacyl 8′-*O*-benzoyl-ML-236A-carboxylate
122. *p*-Methoxyphenacyl 8′-*O*-benzoyl-ML-236A-carboxylate
123. Sodium 8′-*O*-benzoyl-MB-530A-carboxylate
124. Potassium 8′-*O*-benzoyl-MB-530A-carboxylate
125. Aluminium tris(8′-*O*-benzoyl-MB-530A-carboxylate)
126. Methyl 8′-*O*-benzoyl-MB-530A-carboxylate
127. Ethyl 8′-*O*-benzoyl-MB-530A-carboxylate
128. Butyl 8′-*O*-benzoyl-MB-530A-carboxylate
129. Benzyl 8′-*O*-benzoyl-MB-530A-carboxylate
130. *p*-Methoxybenzyl 8′-*O*-benzoyl-MB-530A-carboxylate
131. Phenacyl 8′-*O*-benzoyl-MB-530A-carboxylate

132. *p*-Methoxyphenacyl 8′-*O*-benzoyl-MB-530A-carboxylate
133. Sodium 8′-*O*-(*p*-toluoyl)-ML-236A-carboxylate
134. Calcium bis[8′-*O*-(*p*-toluoyl)-ML-236A-carboxylate]
135. Ethyl 8′-*O*-(*p*-toluoyl)-ML-236A-carboxylate
136. Butyl 8′-*O*-(*p*-toluoyl)-ML-236A-carboxylate
137. Benzyl 8′-*O*-(*p*-toluoyl)-ML-236A-carboxylate
138. Phenacyl 8′-*O*-(*p*-toluoyl)-ML-236A-carboxylate
139. Sodium 8′-*O*-(*p*-toluoyl)-MB-530A-carboxylate
140. Methyl 8′-*O*-(p-toluoyl)-MB-530A-carboxylate
141. Butyl 8′-*O*-(*p*-toluoyl)-MB-530A-carboxylate
142. Benzyl 8′-*O*-(*p*-toluoyl)-MB-530A-carboxylate
143. Phenacyl 8′-*O*-(*p*-toluoyl)-MB-530A-carboxylate
144. Sodium 8′-*O*-(2-chlorobenzoyl)-ML-236A-carboxylate
145. Sodium 8′-*O*-(2-chlorobenzoyl)-MB-530A-carboxylate
146. Sodium 8′-*O*-(3-chlorobenzoyl)-ML-236A-carboxylate
147. Sodium 8′-*O*-(3-chlorobenzoyl)-MB-530A-carboxylate
148. Sodium 8′-*O*-(4-chlorobenzoyl)-ML-236A-carboxylate
149. Sodium 8′-*O*-(4-chlorobenzoyl)-MB-530A-carboxylate
150. Sodium 8′-*O*-salicyloyl-ML-236A-carboxylate
151. Potassium 8′-*O*-salicyloyl-ML-236A-carboxylate
152. Methyl 8′-*O*-salicyloyl-ML-236A-carboxylate
153. Ethyl 8′-*O*-salicyloyl-ML-236A-carboxylate
154. Butyl 8′-*O*-salicyloyl-ML-236A-carboxylate
155. Benzyl 8′-*O*-salicyloyl-ML-236A-carboxylate
156. Phenacyl 8′-*O*-salicyloyl-ML-236A-carboxylate
157. Sodium 8′-*O*-salicyloyl-MB-530A-carboxylate
158. Potassium 8′-*O*-salicyloyl-MB-530A-carboxylate
159. Methyl 8′-*O*-salicyloyl-MB-530A-carboxylate
160. Ethyl 8′-*O*-salicyloyl-MB-530A-carboxylate
161. Butyl 8′-*O*-salicyloyl-MB-530A-carboxylate
162. Benzyl 8′-*O*-salicyloyl-MB-530A-carboxylate
163. Phenacyl 8′-*O*-salicyloyl-MB-530A-carboxylate
164. Sodium 8′-*O*-phenylacetyl-ML-236A-carboxylate
165. Methyl 8′-*O*-phenylacetyl-ML-236A-carboxylate
166. Ethyl 8′-*O*-phenylacetyl-ML-236A-carboxylate
167. Benzyl 8′-*O*-phenylacetyl-ML-236A-carboxylate
168. Sodium 8′-*O*-phenylacetyl-MB-530A-carboxylate
169. Methyl 8′-*O*-phenylacetyl-MB-530A-carboxylate
170. Ethyl 8′-*O*-phenylacetyl-MB-530A-carboxylate
171. Benzyl 8′-*O*-phenylacetyl-MB-530A-carboxylate
172. Sodium 8′-*O*-cinnamoyl-ML-236A-carboxylate
173. Sodium 8′-*O*-cinnamoyl-MB-530A-carboxylate
174. Sodium 8′-*O*-(*p*-hydroxycinnamoyl)-ML-236A-carboxylate
175. Sodium 8′-*O*-(*p*-hydroxycinnamoyl)-MB-530A-carboxylate
176. Sodium 8′-*O*-cyclohexanecarbonyl-ML-236A-carboxylate
177. Sodium 8′-*O*-cyclohexanecarbonyl-MB-530A-carboxylate
178. Sodium 8′-*O*-(2-thenoyl)-ML-236A-carboxylate
179. Methyl 8′-*O*-(2-thenoyl)-ML-236A-carboxylate
180. Ethyl 8′-*O*-(2-thenoyl)-ML-236A-carboxylate
181. Sodium 8′-*O*-(2-thenoyl)-MB-530A-carboxylate
182. Methyl 8′-*O*-(2-thenoyl)-MB-530A-carboxylate
183. Ethyl 8′-*O*-(2-thenoyl)-MB-530A-carboxylate
184. Sodium 8′-*O*-(2-furoyl)-ML-236A-carboxylate
185. Methyl 8′-*O*-(2-furoyl)-ML-236A-carboxylate
186. Ethyl 8′-*O*-(2-furoyl)-ML-236A-carboxylate
187. Sodium 8′-*O*-(2-furoyl)-MB-530A-carboxylate
188. Methyl 8′-*O*-(2-furoyl)-MB-530A-carboxylate
189. Ethyl 8′-*O*-(2-furoyl)-MB-530A-carboxylate
190. Sodium 8′-*O*-(2-thienylacetyl)-ML-236A-carboxylate
191. Methyl 8′-*O*-(2-thienylacetyl)-ML-236A-carboxylate
192. Ethyl 8′-*O*-(2-thienylacetyl)-ML-236A-carboxylate
193. Butyl 8′-*O*-(2-thienylacetyl)-ML-236A-carboxylate
194. Benzyl 8′-*O*-(2-thienylacetyl)-ML-236A-carboxylate
195. Phenacyl 8′-*O*-(2-thienylacetyl)-ML-236A-carboxylate
196. Sodium 8′-*O*-(2-thienylacetyl)-MB-530A-carboxylate

197. Methyl 8′-*O*-(2-thienylacetyl)-MB-530A-carboxylate
198. Ethyl 8′-*O*-(2-thienylacetyl)-MB-530A-carboxylate
199. Sodium 8′-*O*-methanesulphonyl-ML-236A-carboxylate
200. Methyl 8′-*O*-methanesulphonyl-ML-236A-carboxylate
201. Ethyl 8′-*O*-methanesulphonyl-ML-236A-carboxylate
202. Sodium 8′-*O*-methanesulphonyl-MB-530A-carboxylate
203. Methyl 8′-*O*-methanesulphonyl-MB-530A-carboxylate
204. Ethyl 8′-*O*-methanesulphonyl-MB-530A-carboxylate
205. Trisodium 8′-*O*-phosphoryl-ML-236A-carboxylate
206. Trisodium 8′-*O*-phosphoryl-MB-530A-carboxylate
207. Sodium 3-*O*-acetyl-ML-236A-carboxylate
208. Methyl 3-*O*-acetyl-ML-236A-carboxylate
209. Ethyl 3-*O*-acetyl-ML-236A-carboxylate
210. Butyl 3-*O*-acetyl-ML-236A-carboxylate
211. Benzyl 3-*O*-acetyl-ML-236A-carboxylate
212. Sodium 3-*O*-acetyl-MB-530A-carboxylate
213. Methyl 3-*O*-acetyl-MB-530A-carboxylate
214. Butyl 3-*O*-acetyl-MB-530A-carboxylate
215. Benzyl 3-*O*-acetyl-MB-530A-carboxylate
216. Sodium 3-*O*-butyryl-ML-236A-carboxylate
217. Methyl 3-*O*-butyryl-ML-236A-carboxylate
218. Butyl 3-*O*-butyryl-ML-236A-carboxylate
219. Benzyl 3-*O*-butyryl-ML-236A-carboxylate
220. Sodium 3-*O*-butyryl-MB-530A-carboxylate
221. Methyl 3-*O*-butyryl-MB-530A-carboxylate
222. Ethyl 3-*O*-butyryl-MB-530A-carboxylate
223. Benzyl 3-*O*-butyryl-MB-530A-carboxylate
224. Sodium 3-*O*-benzoyl-ML-236A-carboxylate
225. Methyl 3-*O*-benzoyl-ML-236A-carboxylate
226. Ethyl 3-*O*-benzoyl-ML-236A-carboxylate
227. Butyl 3-*O*-benzoyl-ML-236A-carboxylate
228. Benzyl 3-*O*-benzoyl-ML-236A-carboxylate
229. Sodium 3-*O*-benzoyl-MB-530A-carboxylate
230. Methyl 3-*O*-benzoyl-MB-530A-carboxylate
231. Ethyl 3-*O*-benzoyl-MB-530A-carboxylate
232. Butyl 3-*O*-benzoyl-MB-530A-carboxylate
233. Benzyl 3-*O*-benzoyl-MB-530A-carboxylate
234. Sodium 3,8′-di(*O*-acetyl)-ML-236A-carboxylate
235. Methyl 3,8′-di(*O*-acetyl)-ML-236A-carboxylate
236. Ethyl 3,8′-di(*O*-acetyl)-ML-236A-carboxylate
237. Benzyl 3,8′-di(*O*-acetyl)-ML-236A-carboxylate
238. Sodium 3,8′-di(*O*-acetyl)-MB-530A-carboxylate
239. Methyl 3,8′-di-(*O*-acetyl)-MB-530A-carboxylate
240. Butyl 3,8′-di(*O*-acetyl)-MB-530A-carboxylate
241. Benzyl 3,8′-di(*O*-acetyl)-MB-530A-carboxylate
242. Sodium 3,8′-di(*O*-butyryl)-ML-236A-carboxylate
243. Methyl 3,8′-di(*O*-butyryl)-ML-236A-carboxylate
244. Butyl 3,8′-di(*O*-butyryl)-ML-236A-carboxylate
245. Benzyl 3,8′-di(*O*-butyryl)-ML-236A-carboxylate
246. Sodium 3,8′-di(*O*-butyryl)-MB-530A-carboxylate
247. Methyl 3,8′-di(*O*-butyryl)-MB-530A-carboxylate
248. Butyl 3,8′-di(*O*-butyryl)-MB-530A-carboxylate
249. Benzyl 3,8′-di(*O*-butyryl)-MB-530A-carboxylate
250. Sodium 3,8′-di(*O*-benzoyl)-ML-236A-carboxylate
251. Methyl 3,8′-di(*O*-benzoyl)-ML-236A-carboxylate
252. Ethyl 3,8′-di-(*O*-benzoyl)-ML-236A-carboxylate
253. Butyl 3,8′-di(*O*-benzoyl)-ML-236A-carboxylate
254. Benzyl 3,8′-di(*O*-benzoyl)-ML-236A-carboxylate
255. Sodium 3,8′-di(*O*-benzoyl)-MB-530A-carboxylate
256. Methyl 3,8′-di(*O*-benzoyl)-MB-530A-carboxylate
257. Butyl 3,8′-di(*O*-benzoyl)-MB-530A-carboxylate
258. Benzyl 3,8′-di(*O*-benzoyl)-MB-530A-carboxylate
259. Sodium 3-*O*-acetyl-8′-*O*-butyryl-ML-236A-carboxylate
260. Sodium 3-*O*-acetyl-8′-*O*-butyryl-MB-530A-carboxylate
261. Sodium 3-*O*-butyryl-8′-*O*-acetyl-ML-236A-carboxylate

262. Sodium 3-*O*-butyryl-8′-*O*-acetyl-MB-530A-carboxylate
263. Sodium 3-*O*-benzoyl-8′-*O*-acetyl-ML-236A-carboxylate
264. Sodium 3-*O*-benzoyl-8′-*O*-acetyl-MB-530A-carboxylate
265. Sodium 3-*O*-benzoyl-8′-*O*-butyryl-ML-236A-carboxylate
266. Sodium 3-*O*-benzoyl-8′-*O*-butyryl-MB-530A-carboxylate
267. Sodium 3-*O*-acetyl-8′-*O*-benzoyl-ML-236A-carboxylate
268. Sodium 3-*O*-acetyl-8′-*O*-benzoyl-MB-530A-carboxylate
269. Sodium 3-*O*-butyryl-8′-*O*-benzoyl-ML-236A-carboxylate
270. Sodium 3-*O*-butyryl-8′-*O*-benzoyl-MB-530A-carboxylate
271. Sodium 3,5,8′-tri(*O*-acetyl)-ML-236A-carboxylate
272. Potassium 3,5,8′-tri(*O*-acetyl)-ML-236A-carboxylate
273. Methyl 3,5,8′-tri(*O*-acetyl)-ML-236A-carboxylate
274. Ethyl 3,5,8′-tri(*O*-acetyl)-ML-236A-carboxylate
275. Butyl 3,5,8′-tri(*O*-acetyl)-ML-236A-carboxylate
276. Benzyl 3,5,8′-tri(*O*-acetyl)-ML-236A-carboxylate
277. Phenacyl 3,5,8′-tri(*O*-acetyl)-ML-236A-carboxylate
278. Sodium 3,5,8′-tri(*O*-butyryl)-ML-236A-carboxylate
279. Methyl 3,5,8′-tri(*O*-butyryl)-ML-236A-carboxylate
280. Ethyl 3,5,8′-tri(*O*-butyryl)-ML-236A-carboxylate
281. Butyl 3,5,8′-tri(*O*-butyryl)-ML-236A-carboxylate
282. Benzyl 3,5,8′-tri(*O*-butyryl)-ML-236A-carboxylate
283. Pivaloyloxymethyl 3,5,8′-tri(*O*-butyryl)-ML-236A-carboxylate
284. Phenacyl 3,5,8′-tri(*O*-butyryl)-ML-236A-carboxylate
285. Sodium 3,5,8′-tri(*O*-butyryl)-MB-530A-carboxylate
286. Potassium 3,5,8′-tri(*O*-butyryl)-MB-530A-carboxylate
287. Methyl 3,5,8′-tri(*O*-butyryl)-MB-530A-carboxylate
288. Ethyl 3,5,8′-tri(*O*-butyryl)-MB-530A-carboxylate
289. Butyl 3,5,8′-tri(*O*-butyryl)-MB-530A-carboxylate
290. Benzyl 3,5,8′-tri(*O*-butyryl)-MB-530A-carboxylate
291. Pivaloyloxymethyl 3,5,8′-tri(*O*-butyryl)-M-530A-carboxylate
292. Phenacyl 3,5,8′-tri(*O*-butyryl)-MB-530A-carboxylate
293. Sodium 3,5-di(*O*-acetyl)-ML-236B-carboxylate
294. Potassium 3,5-di(*O*-acetyl)-ML-236B-carboxylate
295. Aluminium tris[3,5-di(*O*-acetyl)-ML-236B-carboxylate]
296. Calcium bis[3,5-di(*O*-acetyl)-ML-236B-carboxylate]
297. Methyl 3,5-di(*O*-acetyl)-ML-236B-carboxylate
298. Ethyl 3,5-di(*O*-acetyl)-ML-236B-carboxylate
299. Isopropyl 3,5-di(*O*-acetyl)-ML-236B-carboxylate
300. Butyl 3,5-di(*O*-acetyl)-ML-236B-carboxylate
301. Benzyl 3,5-di(*O*-acetyl)-ML-236B-carboxylate
302. Pivaloyloxymethyl 3,5-di(*O*-acetyl)-ML-236B-carboxylate
303. Ethoxymethyl 3,5-di(*O*-acetyl)-ML-236B-carboxylate
304. Phenacyl 3,5-di(*O*-acetyl)-ML-236B-carboxylate
305. Sodium 3,5-di(*O*-acetyl)-MB-530B-carboxylate
306. Potassium 3,5-di(*O*-acetyl)-MB-530B-carboxylate
307. Calcium bis[3,5-di(*O*-acetyl)-MB-530B-carboxylate]
308. Aluminium tri[3,5-di(*O*-acetyl)-MB-530B-carboxylate]
309. Methyl 3,5-di(*O*-acetyl)-MB-530B-carboxylate
310. Ethyl 3,5-di(*O*-acetyl)-MB-530B-carboxylate
311. Isopropyl 3,5-di(*O*-acetyl)-MB-530B-carboxylate
312. Butyl 3,5-di(*O*-acetyl)-MB-530B-carboxylate
313. Benzyl 3,5-di(*O*-acetyl)-MB-530B-carboxylate
314. Pivaloyloxymethyl 3,5-di(*O*-acetyl)-MB-530B-carboxylate
315. Methoxymethyl 3,5-di(*O*-acetyl)-MB-530B-carboxylate
316. Ethoxymethyl 3,5-di(*O*-acetyl)-MB-530B-carboxylate
317. Phenacyl 3,5-di(*O*-acetyl)-MB-530B-carboxylate
318. Sodium 3,5-di(*O*-propionyl)-ML-236B-carboxylate
319. Methyl 3,5-di(*O*-propionyl)-ML-236B-carboxylate
320. Butyl 3,5-di(*O*-propionyl)-ML-236B-carboxylate
321. Benzyl 3,5-di(*O*-propionyl)-ML-236B-carboxylate
322. Sodium 3,5-di(*O*-propionyl)-MB-530B-carboxylate
323. Methyl 3,5-di(*O*-propionyl)-MB-530B-carboxylate
324. Butyl 3,5-di(*O*-propionyl)-MB-530B-carboxylate
325. Benzyl 3,5-di(*O*-propionyl)-MB-530B-carboxylate
326. Sodium 3,5-di(*O*-butyryl)-ML-236B-carboxylate

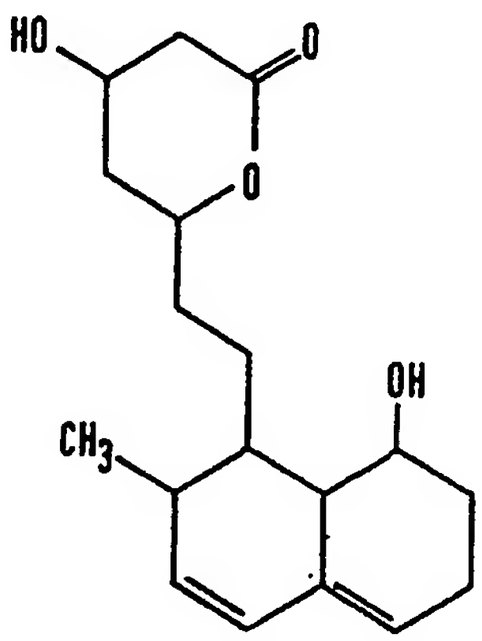
327. Methyl 3,5-di(*O*-butyryl)-ML-236B-carboxylate
328. Sodium 3,5-di(*O*-butyryl)-MB-530B-carboxylate
329. Methyl 3,5-di(*O*-butyryl)-MB-530B-carboxylate
330. Sodium 3,5-di(*O*-valeryl)-ML-236B-carboxylate
331. Potassium 3,5-di(*O*-valeryl)-ML-236B-carboxylate
332. Sodium 3,5-di(*O*-valeryl)-MB-530B-carboxylate
333. Potassium 3,5-di(*O*-valeryl)-MB-530B-carboxylate
334. Sodium 3,5-di(*O*-isovaleryl)-ML-236B-carboxylate
335. Sodium 3,5-di(*O*-isovaleryl)-MB-530B-carboxylate
336. Sodium 3,5-di(*O*-stearoyl)-ML-236B-carboxylate
337. Sodium 3,5-di(*O*-stearoyl)-MB-530B-carboxylate
338. Sodium 3,5-di(*O*-oleoyl)-ML-236B-carboxylate
339. Sodium 3,5-di(*O*-linoleoyl)-ML-236B-carboxylate
340. Sodium 3,5-di(*O*-linoleoyl)-MB-530B-carboxylate
341. Sodium 3,5-di(*O*-benzoyl)-ML-236B-carboxylate
342. Sodium 3,5-di(*O*-benzoyl)-MB-530B-carboxylate
343. Sodium 3,5-di(*O*-phenylacetyl)-ML-236B-carboxylate
344. Methyl 3,5-di(*O*-phenylacetyl)-ML-236B-carboxylate
345. Sodium 3,5-di(*O*-phenylacetyl)-MB-530B-carboxylate
346. Methyl 3,5-di(*O*-phenylacetyl)-MB-530B-carboxylate
347. Sodium 3,5-di(*O*-cyclopentanecarbonyl)-ML-236B-carboxylate
348. Sodium 3,5-di(*O*-cyclopentanecarbonyl)-MB-530B-carboxylate
349. Sodium 3,5-di(*O*-cyclohexanecarbonyl)-ML-236B-carboxylate
350. Sodium 3,5-di(*O*-cyclohexanecarbonyl)-MB-530B-carboxylate
351. Sodium 3,5-di(*O*-thenoyl)-ML-236B-carboxylate
352. Sodium 3,5-di(*O*-thenoyl)-MB-530B-carboxylate
353. Sodium 3,5-di(*O*-furoyl)-ML-236B-carboxylate
354. Sodium 3,5-di(*O*-furoyl)-MB-530B-carboxylate
355. Sodium 3,5-di(*O*-thienylacetyl)-ML-236B-carboxylate
356. Sodium 3,5-di(*O*-thienylacetyl)-MB-530B-carboxylate
357. Sodium 3,5-di(*O*-methanesulphonyl)-ML-236B-carboxylate
358. Sodium 3,5-di(*O*-methanesulphonyl)-MB-530B-carboxylate
359. Trisodium 3,5-di(*O*-phosphoryl)-ML-236B-carboxylate
360. Trisodium 3,5-di(*O*-phosphoryl)-MB-530B-carboxylate
361. Sodium 3,5-di(*O*-acetyl)-8′-*O*-propionyl-ML-236A-carboxylate
362. Methyl 3,5-di(*O*-acetyl)-8′-*O*-propionyl-ML-236A-carboxylate
363. Butyl 3,5-di(*O*-acetyl)-8′-*O*-propionyl-ML-236A-carboxylate
364. Benzyl 3,5-di(*O*-acetyl)-8′-*O*-propionyl-ML-236A-carboxylate
365. Sodium 3,5-di(*O*-acetyl)-8′-*O*-propionyl-MB-530A-carboxylate
366. Methyl 3,5-di(*O*-acetyl)-8′-*O*-propionyl-MB-530A-carboxylate
367. Sodium 3,5-di(*O*-acetyl)-8′-*O*-butyryl-ML-236A-carboxylate
368. Methyl 3,5-di(*O*-acetyl)-8′-*O*-butyryl-ML-236A-carboxylate
369. Butyl 3,5-di(*O*-acetyl)-8′-*O*-butyryl-ML-236A-carboxylate
370. Sodium 3,5-di(*O*-acetyl)-8′-*O*-butyryl-MB-530A-carboxylate
371. Methyl 3,5-di(*O*-acetyl)-8′-*O*-butyryl-MB-530A-carboxylate
372. Butyl 3,5-di(*O*-acetyl)-8′-*O*-butyryl-MB-530A-carboxylate
373. Sodium 3,5-di(*O*-butyryl)-8′-*O*-acetyl-ML-236A-carboxylate
374. Sodium 3,5-di(*O*-butyryl)-8′-*O*-acetyl-MB-530A-carboxylate
375. Sodium 3,5-di(*O*-acetyl)-8′-*O*-benzoyl-ML-236A-carboxylate
376. Sodium 3,5-di(*O*-acetyl)-8′-*O*-benzoyl-MB-530A-carboxylate
377. Sodium 3,5-di(*O*-benzoyl)-8′-*O*-acetyl-ML-236A-carboxylate
378. Methyl 3,5-di(*O*-benzoyl)-8′-*O*-acetyl-ML-236A-carboxylate
379. Sodium 3,5-di(*O*-benzoyl)-8′-*O*-acetyl-MB-530A-carboxylate
380. Methyl 3,5-di(*O*-benzoyl)-8′-*O*-acetyl-MB-530A-carboxylate

Of these compounds, particularly preferred compounds are the following:
Sodium ML-236A-carboxylate
Sodium MB-530A-carboxylate
Sodium 8′-*O*-butyryl-ML-236A-carboxylate
Sodium 8′-*O*-hexanoyl-ML-236A-carboxylate
Ethyl 8′-*O*-butyryl-ML-236A-carboxylate
Ethyl 8′-*O*-hexanoyl-ML-236A-carboxylate
Butyl 8′-*O*-butyryl-ML-236A-carboxylate
Butyl 8′-*O*-(4-pentenoyl)-ML-236A-carboxylate
Butyl 8′-*O*-isovaleryl-MB-530A-carboxylate

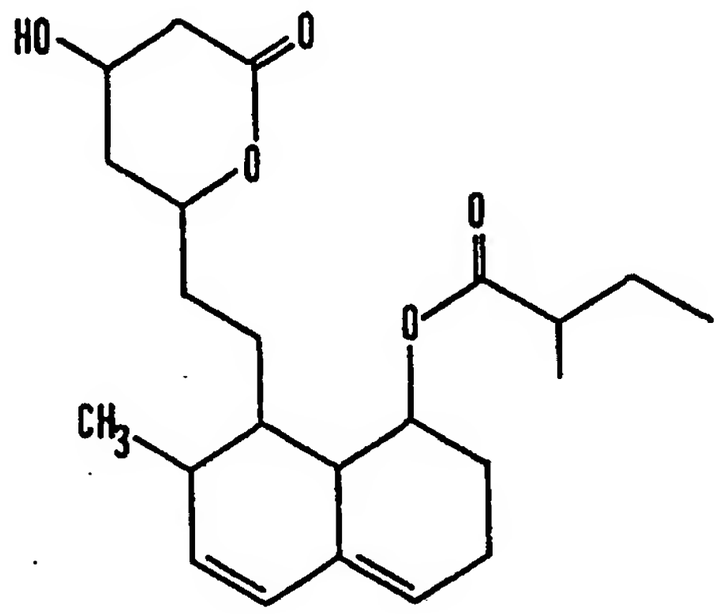
Benzyl 8′-*O*-butyryl-MB-236A-carboxylate
Benzyl 8′-*O*-hexanoyl-ML-236A-carboxylate
Phenacyl 8′-*O*-butyryl-MB-530A-carboxylate
Butyl 3,5-di(*O*-acetyl)-ML-236B-carboxylate
Butyl 3,5-di(*O*-benzoyl)-ML-236B-carboxylate.

The compounds of the invention may be prepared by a variety of processes, all of which ultimately start from ML-236A, MB-236B, MB-530A, MB-530B, ML-236A carboxylic acid and MB-530A carboxylic acid, all of which may be prepared by cultivating appropriate microorganisms as described in the prior art hereinbefore referred to and as specifically illustrated hereafter in the Preparations. The chemical structures of these compounds are as follows:

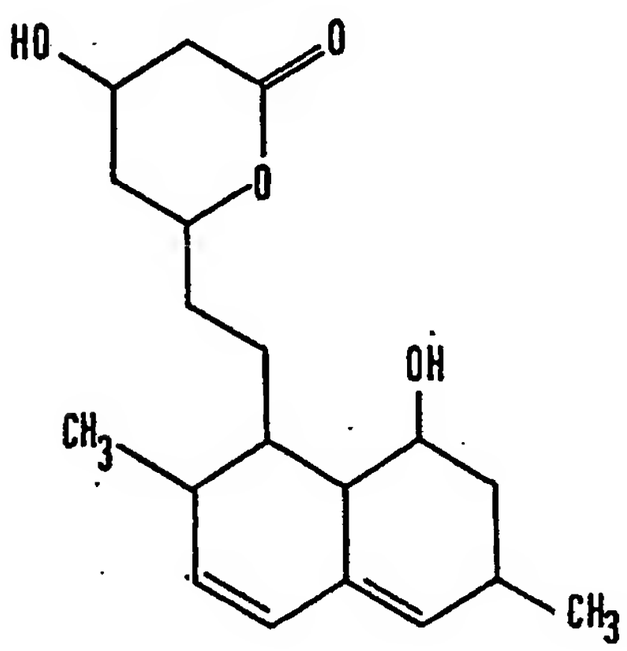
ML-236A



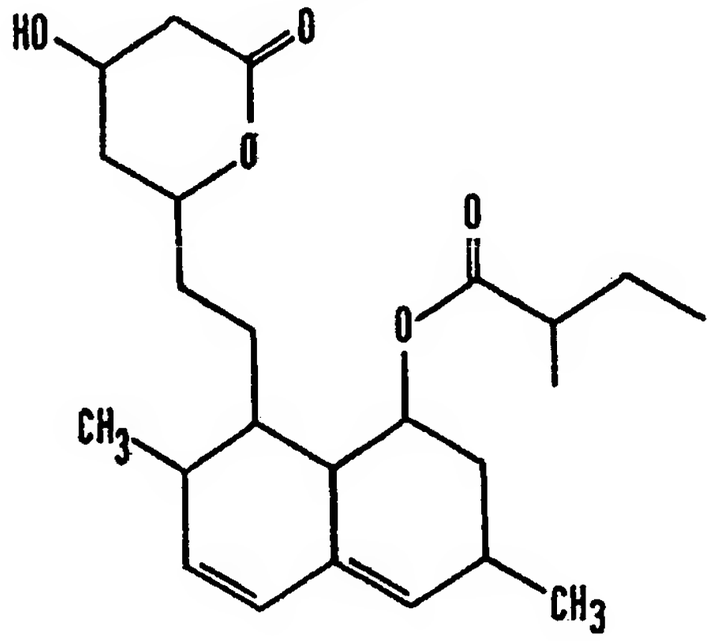
ML-236B



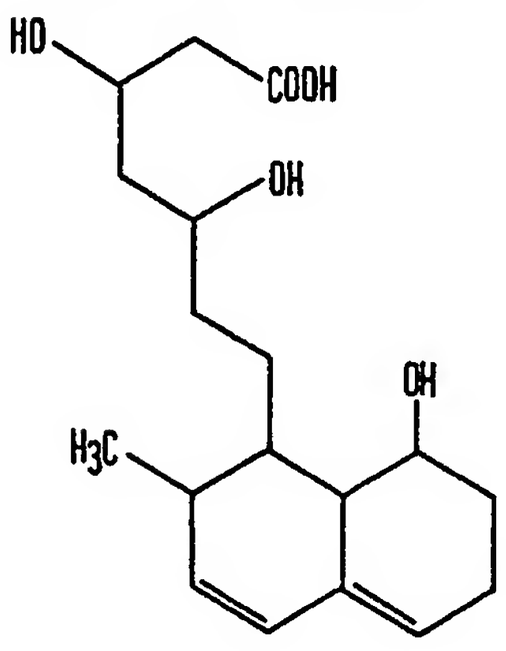
ML-530A



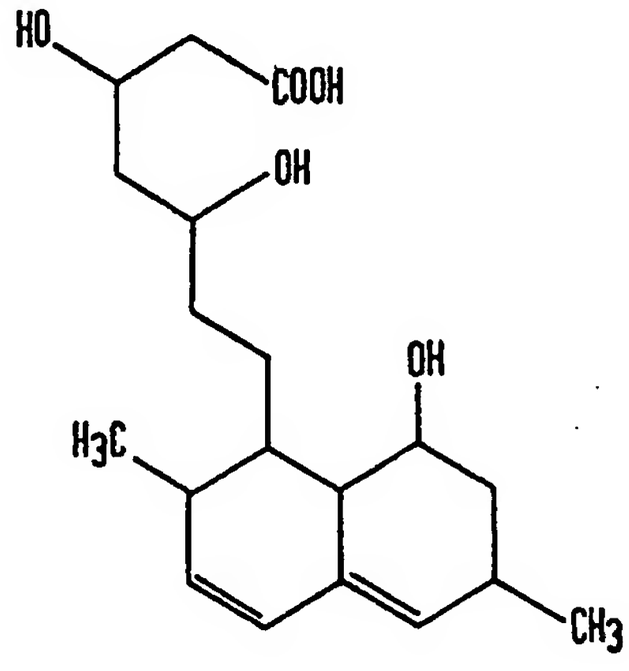
MB-530B



ML-236A carboxylic acid



MB-530A carboxylic acid



Metal salts, and especially the alkali metal salts, of ML-236A and MB-530A may be prepared by cultivating an appropriate microorganism and then recovering the desired salt from the culture broth.

Specifically, salts of ML-236A carboxylic acid may be prepared by cultivating an ML-236A-producing microorganism of the genus *Penicillium* and recovering the ML-236A carboxylic acid salt from the culture broth, whilst MB-530A carboxylic acid salts may be prepared by cultivating an MB-530A- producing microorganism of the genus *Monascus* and recovering the MB-530A carboxylic acid salt from the culture broth.

The microorganisms of the genus *Penicillium* are preferably *Penicillium citrinum, Penicillium chrysogenum* or *Penicillium notatum*, most preferably *Penicillium citrinum* SANK 18767 (FERM 2609), *Penicillium citrinum* SANK 24467, *Penicillium citrinum* SANK 24567, *Penicillium chrysogenum* SANK 12768 (ATCC 10002) or *Penicillium notatum* SANK 24867.

The microorganisms of the genus *Monascus* are preferably strains of *Monascus ruber, Monascus anka, Monascus paxii, Monascus purpureus* or *Monascus vitreus*, preferably *Monascus ruber* SANK 11272 (IFO 9203), *Monascus ruber* SANK 17075 (CBS 832.70), *Monascus ruber* SANK 17175 (CBS 503.70), *Monascus ruber* SANK 17275 (ATCC 18199), *Monascus ruber* SANK 15177 (FERM 4956), *Monascus ruber* SANK 13778 (FERM 4959), *Monascus ruber* SANK 10671 (FERM 4958), *Monascus ruber* SANK 18174 (FERM 4957), *Monascus anka* SANK 10171 (IFO 6540), *Monascus paxli* SANK 11172 (IFO 8201), *Monascus purpureus* SANK 10271 (IFO 4513) or *Monascus vitreus* SANK 10960 (NIHS 609, e-609, FERM 4960).

All of these microorganisms are available from recognized culture collections, as indicated by the following codes:

IFO =Institute for Fermentation, Osaka, Japan;
FERM =Fermentation Research Institute, Agency of Industrial Science and Technology, Ministry of International Trade and Industry, Japan;
NIHS =National Institute of Hygenic Sciences, Japan;
CBS =Centraal Bureau Voor Schimmelcultures, Netherlands,
ATCC =American Type Culture Collection, Maryland, U.S.A.

Apart from the strains of microorganisms mentioned above, any microorganism of the genus *Penicillium* or *Monascus*, including varieties and mutants, which are capable of producing ML-236A or MB-530A, respectively, may be employed in the process of the present invention.

The ML-236A and MB-530A salts may be produced by cultivating the chosen microorganism in a culture broth under aerobic conditions, using the techniques well-known in the art for cultivation of fungi and other microorganisms. For example, the chosen strain of *Penicillium* or *Monascus* may first be cultivated on a suitable medium and then the produced microorganism may be collected and inoculated into and cultivated on another culture medium to produce the desired ML-236A or MB-530A; the culture medium used for the multiplication of the microorganism and the culture medium used for the production of the ML-236A or MB-530A may be the same or different. Any culture medium well-known in the art for the cultivation of fungi may be employed, provided that it contains, as is well-known, the necessary nutrient materials, especially an assimilable carbon source and an assimilable nitrogen source. Examples of suitable sources of assimilable carbon are glucose, maltose, dextrin, starch, lactose, sucrose and glycerine. Of these sources, glucose and glycerine are particularly preferred for the production of ML-236A and MB-530A. Examples of suitable sources of assimilable nitrogen are peptone, meat extract, yeast, yeast extract, soybean meal, peanut meal, corn steep liquor, rice bran and inorganic nitrogen sources. When producing the ML-236A or MB-530A, an inorganic salt and/or a metal salt may, if necessary, be added to the culture medium. Furthermore, if necessary, a minor amount of a heavy metal may also be added. In certain cases, it is believed possible that the fungus of the genus *Penicillium* or *Monascus* may produce the desired ML-236A or MB-530A carboxylic acid salt directly, whilst in other cases the fungus will produce the ML-236A or MB-530A first and this is then converted to the desired salt in the course of a routine separation and purification procedure. Where the salts are to be produced directly by the fungus, it is important that there should be present in the culture medium or within the body of the fungus metal ions corresponding to the metal salt which it is desired to produce.

The microorganism is preferably cultivated under aerobic conditions using cultivation methods well-known in the art, for example solid culture, shaken culture or culture under aeration and agitation. The microorganisms will grow over a wide temperature range, e.g. from 7 to 35°C, but, especially when the microorganism is grown for the purpose of producing ML-236A or MB-530A or a carboxylic acid salt thereof, the more preferred cultivation temperature is within the range from 20 to 30°C.

During the cultivation of the microorganism, the production of the desired ML-236A or MB-530A or carboxylic acid salt thereof may be monitored by sampling the culture medium and measuring the physiological activity of the medium by appropriate tests. Cultivation may then be continued until a substantial accumulation of active material has been achieved in the culture medium, at which time the ML-236A or MB-530A carboxylic acid salt may be isolated and recovered from the culture medium and the tissues of the microorganism by any suitable combination of isolation techniques,

chosen having regard to their physical and chemical properties. For example, any or all of the following isolation techniques may be employed: extraction of the liquor from the culture broth with a hydrophilic solvent (such as diethyl ether, ethyl acetate or chloroform); extraction of the organism with a hydrophilic solvent (such as acetone or an alcohol); concentration, e.g. by evaporating off all or part of the solvent under reduced pressure; dissolution into a more polar solvent (such as an acetone or an alcohol); removal of impurities with a less polar solvent (such as petroleum ether or hexane); gel filtration through a column of a material such as "Sephadex" (a registered Trade Mark for a material available from Pharmacia Co. Limited, U.S.A.); absorptive chromatography with active carbon or silica gel; rapid liquid chromatography; conversion to ML-236A or MB-530A itself or its parent acid; direct purification in the form of the metal salt; and other similar methods. By using a suitable combination of these techniques, the desired salt can be isolated from the culture broth as a pure substance.

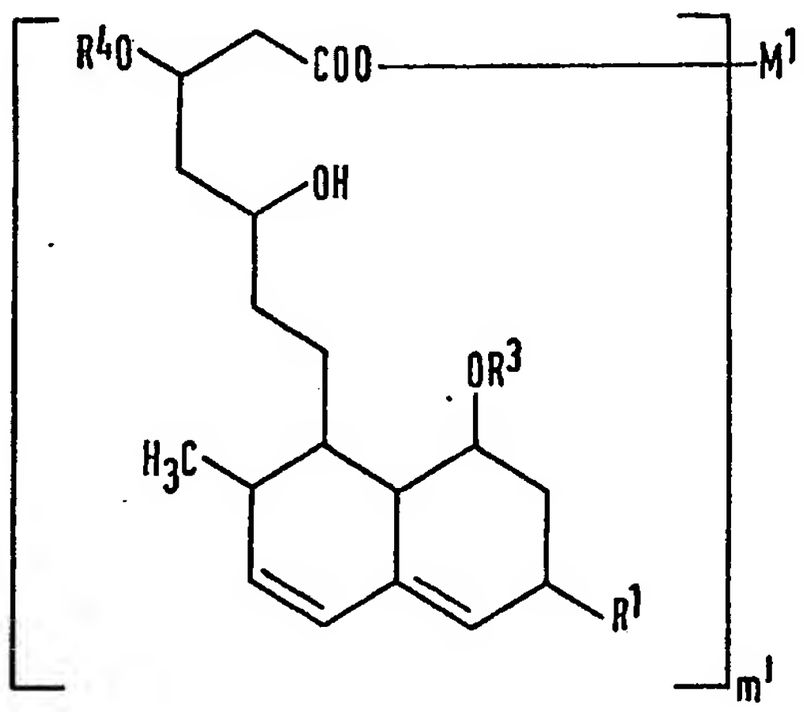
As described in the prior art, ML-236A, ML-236B, MB-530A, MB-530B, ML-236A carboxylic acid and MB-530A carboxylic acid, all of which are important starting materials for the preparation of certain of the compounds of the present invention, may also be produced using the microorganisms and techniques described above.

Others of the compounds of the invention may be prepared by the following methods.

Method 1

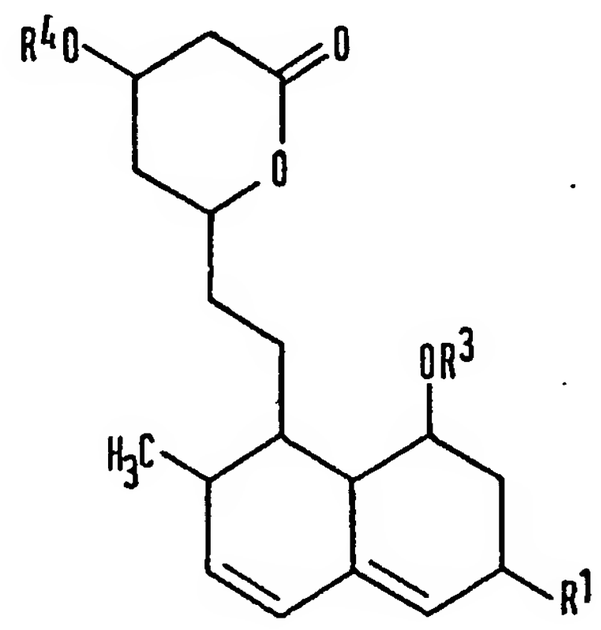
Preparation of Salts

Carboxylic acid salts of formula (IV):



(IV)

(in which R^1, R^3 and R^4 are as defined above; M^1 represents the cationic moiety of a salt; and m' represents the valency of M^1) may be prepared by hydrolyzing a lactone of formula (V):



(V)

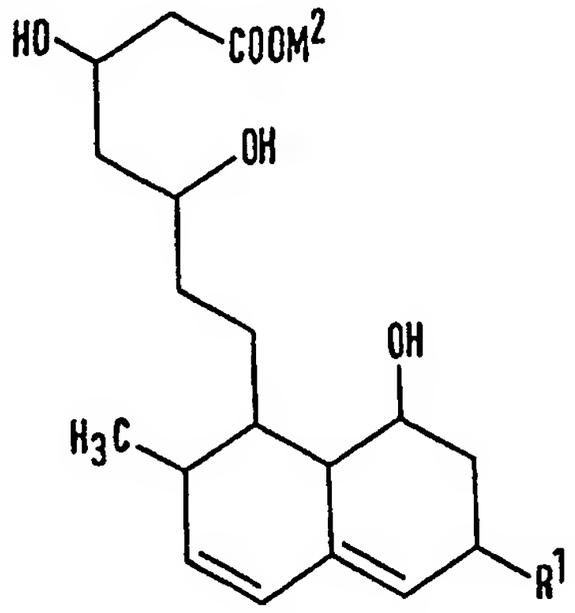
(in which R^1, R^3 and R^4 are as defined above) and, if necessary converting the carboxyl group of the product thus obtained to the corresponding salt.

The hydrolysis may be carried out by any of the methods well-known in the art for conversion of lactones to the corresponding hydroxyacid. If desired, the hydroxyacid may then be extracted with a suitable organic solvent and then salified by reaction with a base corresponding to the salt which it is desired to produce, for example with a metal hydroxide or carbonate, ammonia, organic amine or

amino acid. However, where it is desired to prepare a metal salt (i.e. M^1 represents a metal atom), it is often most convenient to effect the hydrolysis and salification in a single step by using a basic compound of the metal, preferably the metal hydroxide, in an amount at least equimolar with respect to the lactone of formula (V), to effect hydrolysis. In this case, the metal salt of formula (IV) is produced directly and may be obtained simply by distilling off the solvent from the reaction mixture.

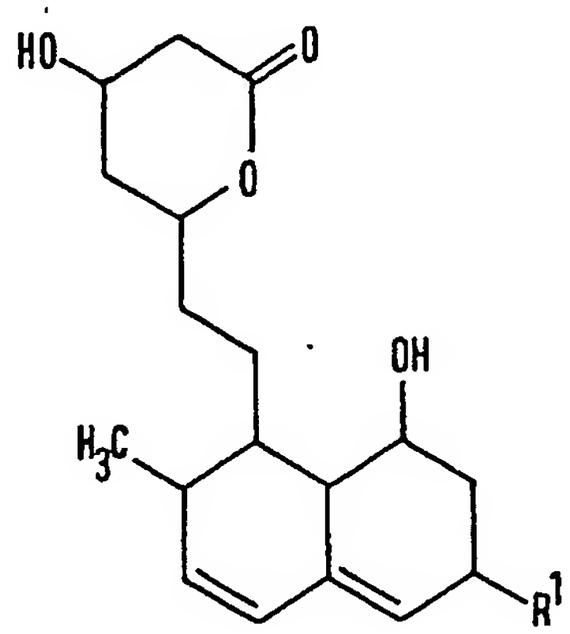
The hydrolysis may be effected by conventional methods, for example by contacting the lactone (V) with a dilute (e.g. from 0.1 to O2N) aqueous solution of the metal hydroxide, preferably an alkali metal hydroxide such as sodium hydroxide or potassium hydroxide, in water or an aqueous organic solution, e.g. an aqueous alcohol or aqueous dioxan. The hydrolysis may be effected over a wide range of temperatures, for example at room temperature or at an elevated temperature, e.g. from 50 to 100°C. The time required for the reaction will vary over a wide range, depending upon the reagents and the reaction temperature, but the reaction will normally require several hours.

In a preferred embodiment of this Method an alkali metal salt of formula (VI):



(VI)

(in which R^1 is as defined above and M^2 represents an alkali metal atom) may be prepared by hydrolyzing, in an alkaline solution containing said alkali metal atom, a lactone of formula (VII):

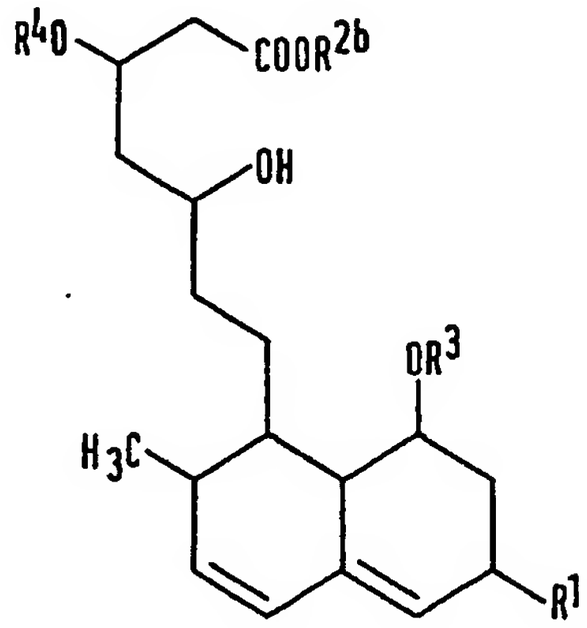


(VII)

(in which R^1 is as defined above). In this case, M^2 preferably represents a sodium atom and the alkaline solution is preferably an aqueous solution of sodium hydroxide.

Method 2
Preparation of Ester from The Corresponding Lactone

Carboxylic acid esters of formula (VIII):



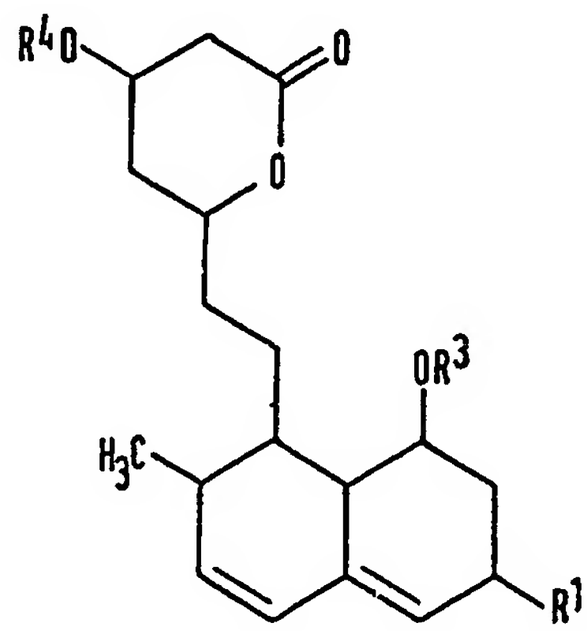
(VIII)

(wherein:

R^1 represents a hydrogen atom or a methyl group;

R^3 and R^4 are the same or different and each represents a hydrogen atom or an acyl group, provided that, when R^3 represents a 2-methylbutyryl group, R^4 represents an acyl group; and

R^{2b} represents an alkyl group or an aralkyl group) may be prepared by reacting a lactone of formula (V):



(V)

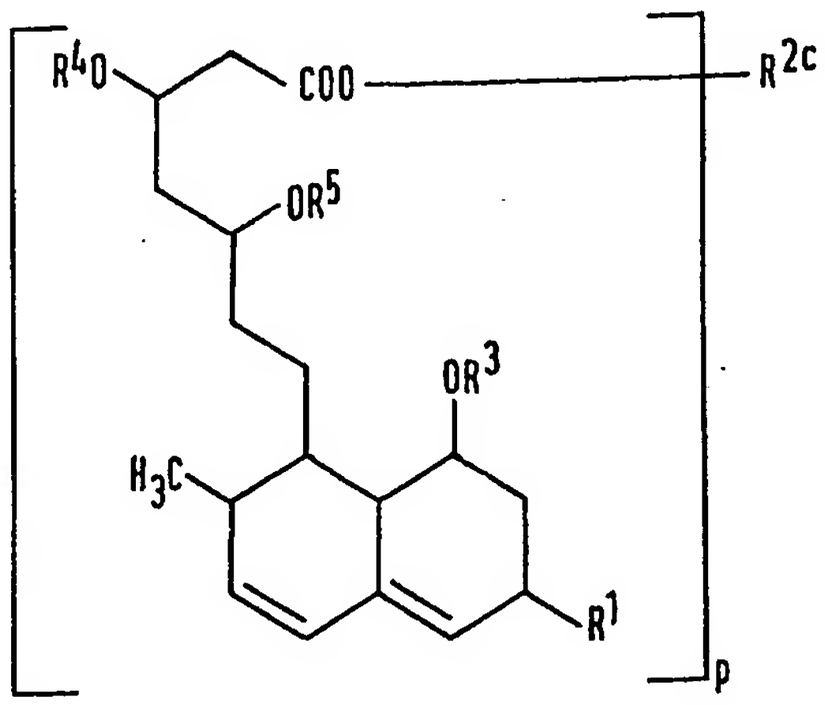
(in which R^1, R^3 and R^4 are as defined above) with an alcohol in the presence of an acid catalyst.

Suitable acid catalysts include: inorganic acids such as hydrochloric acid or sulphuric acid; Lewis acids, such as boron trifluoride; and acidic ion-exchange resins. The reaction may be carried out in the presence of a suitable inert organic solvent, for example benzene, diethyl ether or chloroform. However, where the alcohol, which is one of the reagents, is a liquid, we prefer to use this as the solvent. Although the reaction will take place over a wide temperature range, it is preferably conducted with heating, for example at a temperature of from 50°C to the boiling point of the solvent. After completion of the reaction, the desired product may be recovered from the reaction mixture by conventional methods. For example, when the catalyst employed is an ion-exchange resin, this resin is filtered off and then the solvent is distilled off to give the desired compound. If the catalyst is an inorganic acid or a Lewis acid, this is neutralized and then the solvent is distilled off, the residue is extracted with a suitable solvent, which is then distilled from the extract to give the desired product.

The same process may be employed for the preparation of other esters than alkyl and aralkyl esters, by using appropriate hydroxy- compounds or functional equivalents thereof; for example, compounds of formula (I) where R^2 represents a bivalent aliphatic hydrocarbon group may be prepared by replacing the alcohol used in the above process by a glycol. Also, in place of the acid- catalyzed solvolysis process described above, it is possible to use any other conventional solvolysis technique to produce any compound of formula (I) in which R^2 represents an ester residue capable of formation by solvolysis of a lactone.

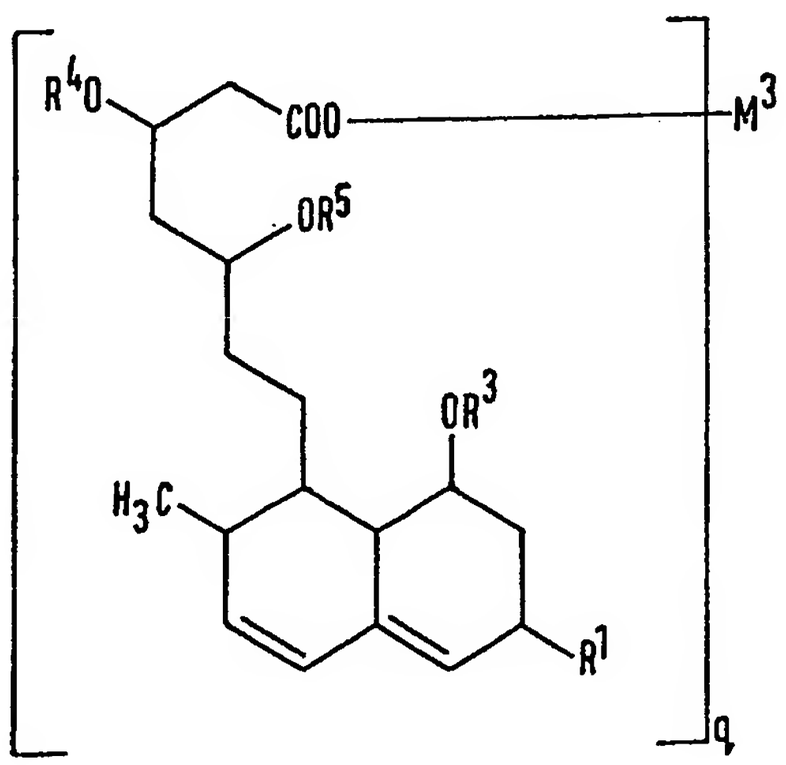
Method 3
Preparation of Esters from The Corresponding Metal Salt

Carboxylic acid esters of formula (IX):



(IX)

(wherein:
R^1, R^3, R^4 and R^5 are as defined above;
R^{2c} represents the alcoholic moiety of an ester; and
p represents the valence of R^{2c})
can be prepared by reacting a metal salt of formula (X):



(X)

(wherein R^1, R^3, R^4 and R^5 are as defined above;
M^3 represents a metal atom, preferably an alkali metal or alkaline earth metal atom; and
q represents the valence of M^3) with an esterifying agent, preferably an esterifying agent of formula R^{2c}—X
(in which X represents a halogen atom, for example a chlorine or bromine atom).

This reaction may be carried out using procedures conventional for alkylating carboxylic acid metal salts. For example, the metal salt of formula (X) may be contacted with the esterifying agent in the presence of an inert organic solvent, to give the desired ester of formula (IX). There is no particular limitation upon the nature of the solvent employed, provided that it has no adverse effect upon the reaction and preferred solvents include dimethylformamide, dimethyl sulphoxide, tetrahydrofuran, hexamethylphosphoryltriamide, acetone and methyl ethyl ketone. The reaction may be carried out over a wide range of temperatures, for example at room temperature or at an elevated temperature, but we normally prefer to carry out the reaction at about room temperature. The time required for the reaction will, of course, depend upon the reaction temperature and upon the reagents employed, but will normally range from 1 to 20 hours. The desired product may be recovered from the reaction mixture by conventional means, for example by diluting the reaction mixture with water, extracting the mixture with a water-immiscible solvent and distilling off the solvent from the extract.

The esterifying agent employed is preferably an alkyl halide, an aralkyl halide or a phenacyl halide and the metal salt of formula (X) is preferably an alkali metal salt (i.e. M^3 represents an alkali metal atom). This alkali metal salt is preferably formed *in situ* by another reaction, for example that described in Method 1, prior to the reaction with the esterifying agent.

It is particularly preferred that the compounds employed should be those compounds in which:

R^1 represents a hydrogen atom or a methyl group;

R^3 represents a hydrogen atom, a C_2—C_6 alkanoyl group or a C_3—C_6 alkenoyl group;

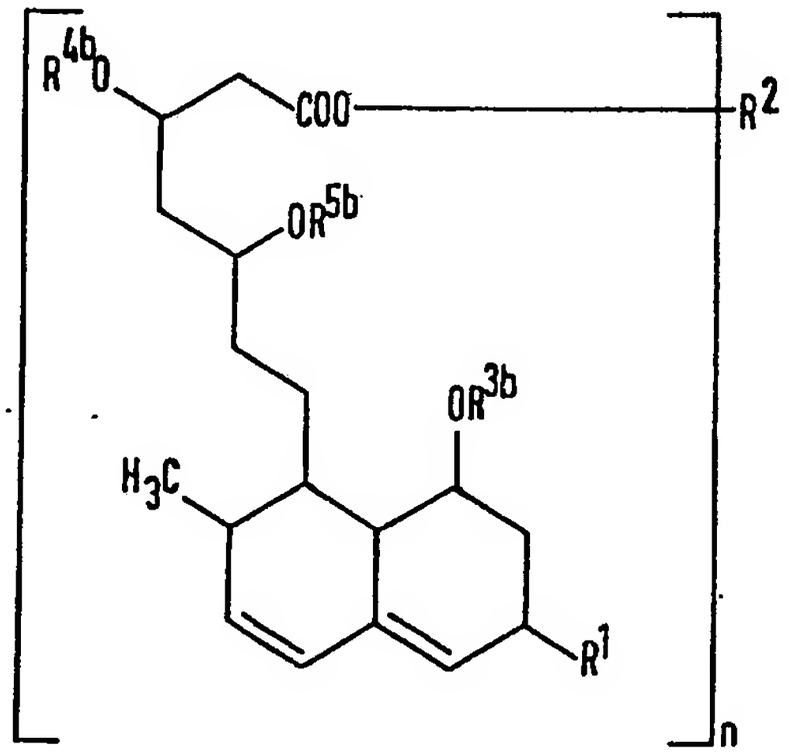
R^4 and R^5 are the same or different and each represents a hydrogen atom, a C_2—C_6 alkanoyl group or a benzoyl group, provided that, when R^3 represents a 2-methylbutyryl group, R^4 and R^5 both represents acyl groups; and

M^3 represents an alkali metal atom; and that the esterifying agent should be a benzyl halide or a phenacyl halide.

Method 4

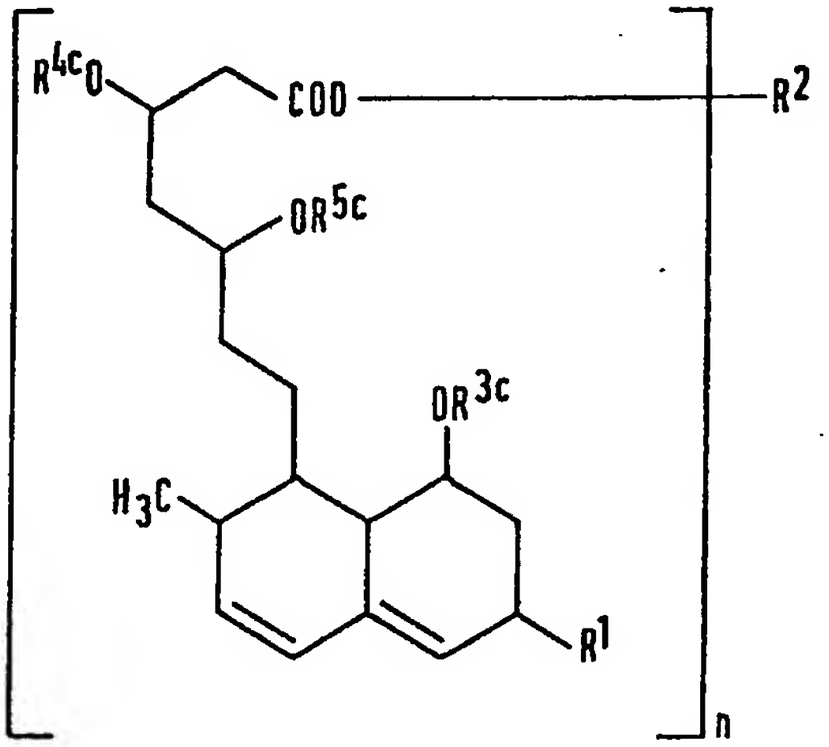
Preparation of 3-acyl, 5-acyl and 8′-acyl Derivatives

A triacyl compound of formula (XI):



(XI)

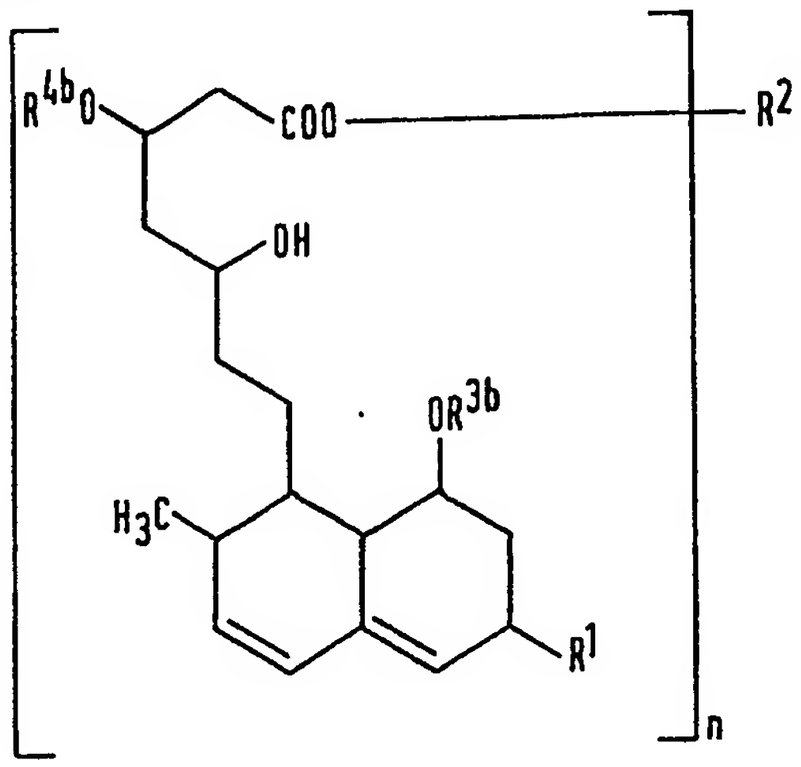
(in which R^1, R^2 and *n* are as defined above and R^{3b}, R^{4b} and R^{5b} are the same or different and each represents an acyl group) may be prepared by acylating a compound of formula (XII):



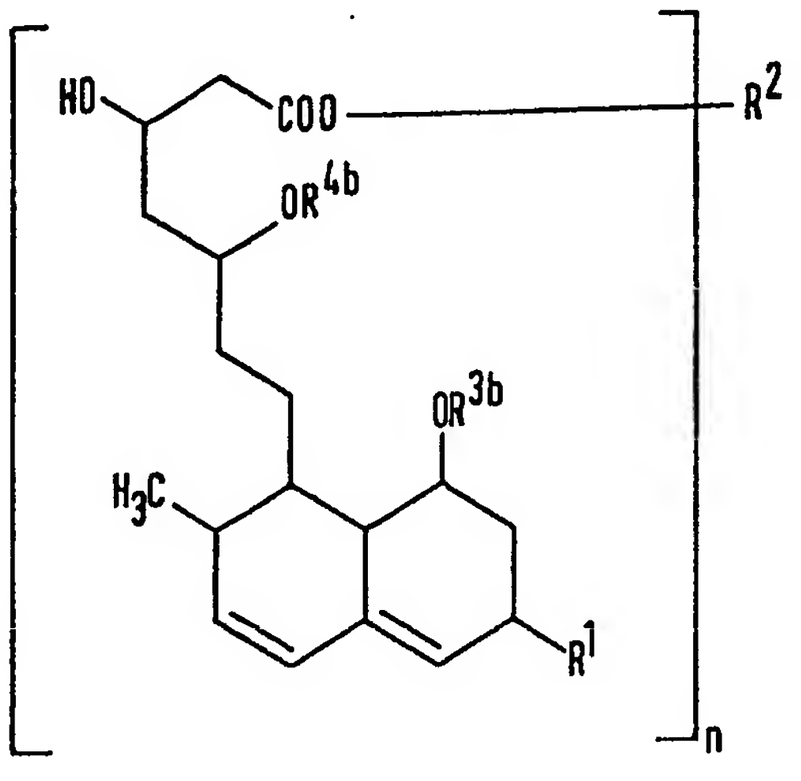
(XII)

(in which R^1, R^2 and *n* are as defined above and R^{3c}, R^{4c} and R^{5c} are the same or different and each represents a hydrogen atom or an acyl group, provided that at least one of R^{3c}, R^{4c} and R^{5c} represents a hydrogen atom).

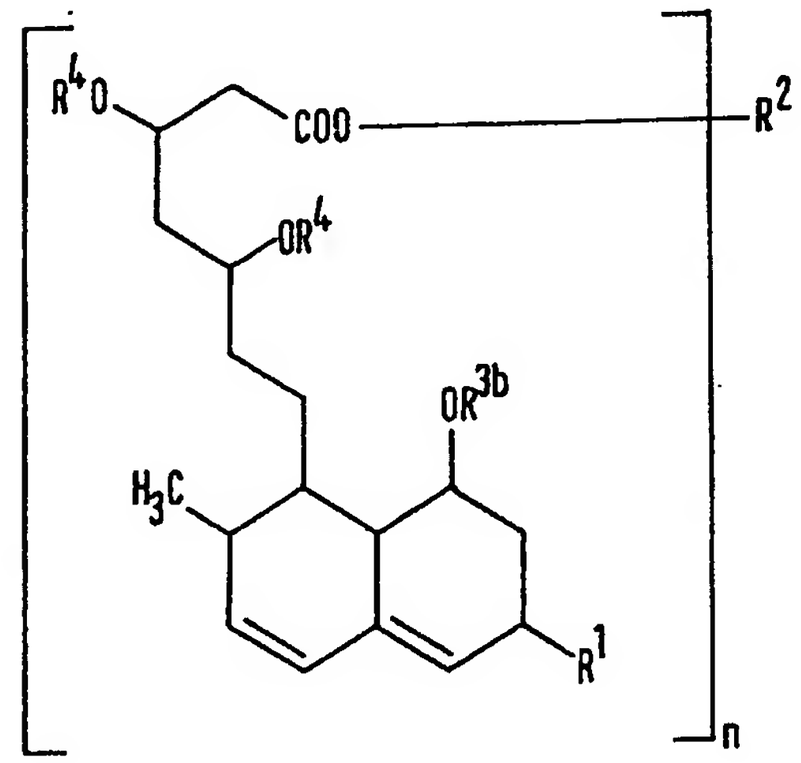
Compounds of formulae (XIII), (XIV) and (XV):



(XIII)



(XIV)



(XV)

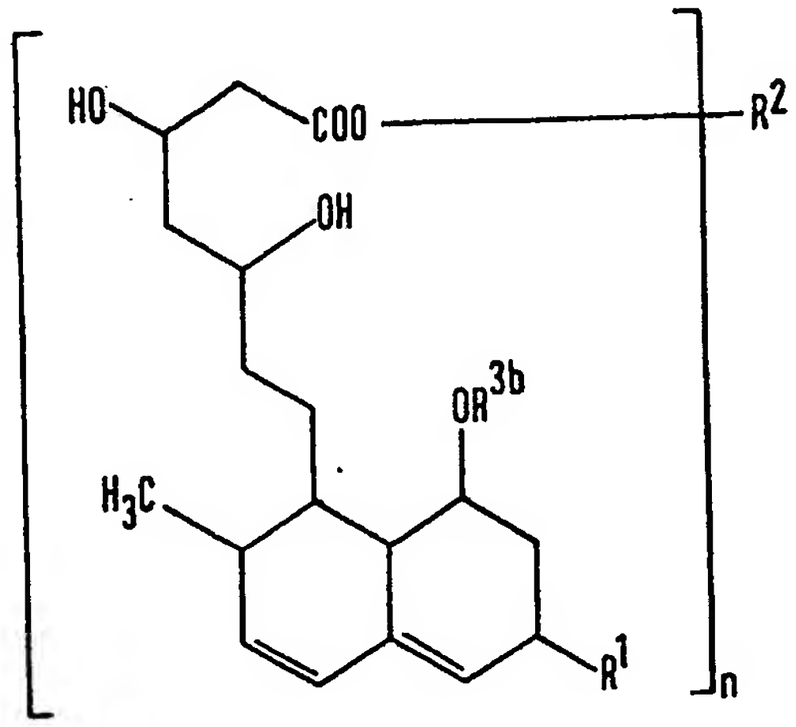
(wherein:

R^1, R^2 and *n* are as defined above;

R^4 represents a hydrogen atom or an acyl group;

R^{3b} represents an acyl group; and

R^{4b} represents an acyl group) may be prepared by acylating a compound of formula (XVI):



(XVI)

(wherein R^1, R^2, *n* and R^{3b} are as defined above). By appropriate choice of conditions, it is possible to prepare either a single one of the compounds of formulae (XIII), (XIV) and (XV), a mixture of any two or a mixture of all three. The desired compound or compounds may then be isolated from the reaction mixture.

The acylation reaction itself is preferably carried out by either of the following processes:

(A) **Acylation Using a Reactive Derivative of An Acid**

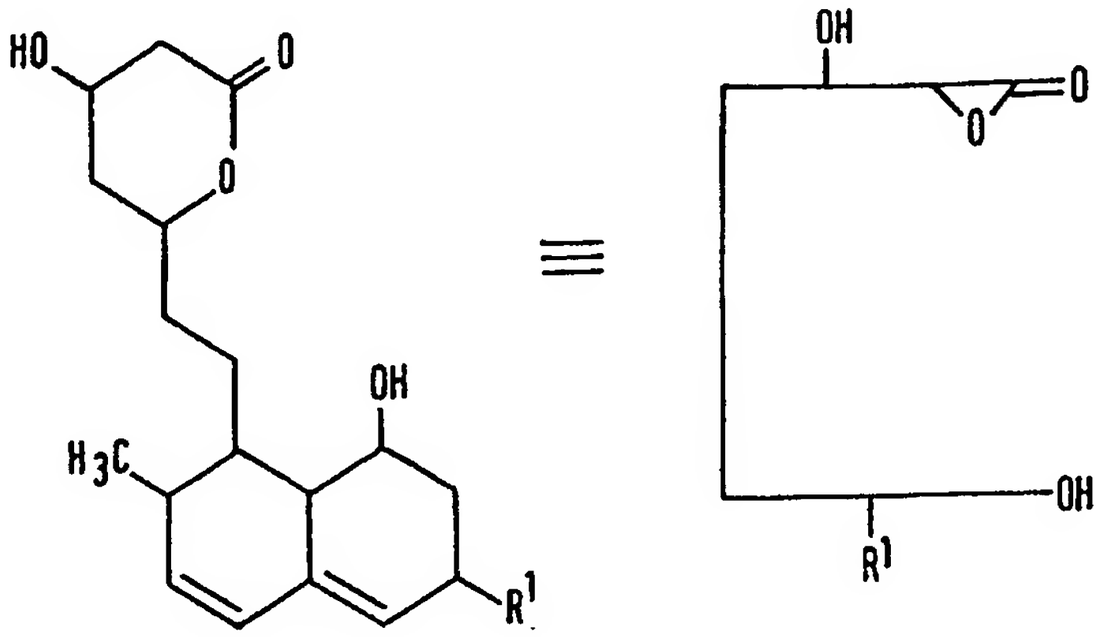
In this process, the compound of formula (XII) or (XVI) is contacted with a reactive derivative of the acid having the desired acyl group, for example an acid halide (such as an acid chloride or acid bromide), an acid anhydride or a mixed acid anhydride (for example a mixed acid anhydride of an acid with a chlorocarbonic ester or a sulphonic acid chloride). The reaction is preferably carried out in the presence of a solvent and also preferably in the presence of a base. There is no particular limitation upon the nature of the solvent to be employed, provided that it has no adverse effect upon the reaction and suitable solvents include chloroform, methylene chloride, diethyl ether, tetrahydrofuran and dioxan. Preferred bases include such organic amines as pyridine, 4-(*N*,*N*-dimethylamino)pyridine, quinoline, triethylamine, *N*-methylmorpholine, *N*-methylpiperidine and *N*,*N*-dimethylaniline. Where the amine employed is a liquid at the reaction temperature, for example pyridine, it may also serve as the solvent. The reaction is preferably carried out at room temperature or with cooling in order to control side reactions, but it will proceed at elevated temperatures. The reaction time will depend upon the reaction temperature and upon the nature of the reagents but it will normally be complete within a period of from 10 minutes to 10 hours. After completion of the reaction, the desired product may be recovered by conventional means, for example by diluting the reaction mixture with water, extracting the mixture with a water-immiscible solvent and distilling the solvent from the extract.

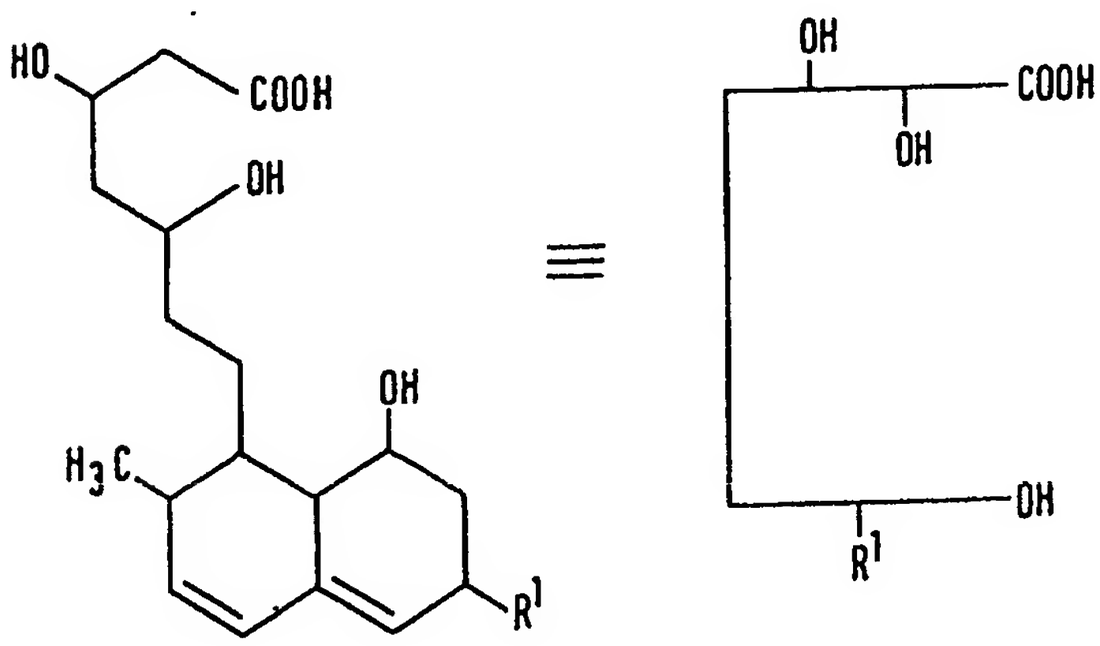
(B) **Acylation With a Condensing Agent**

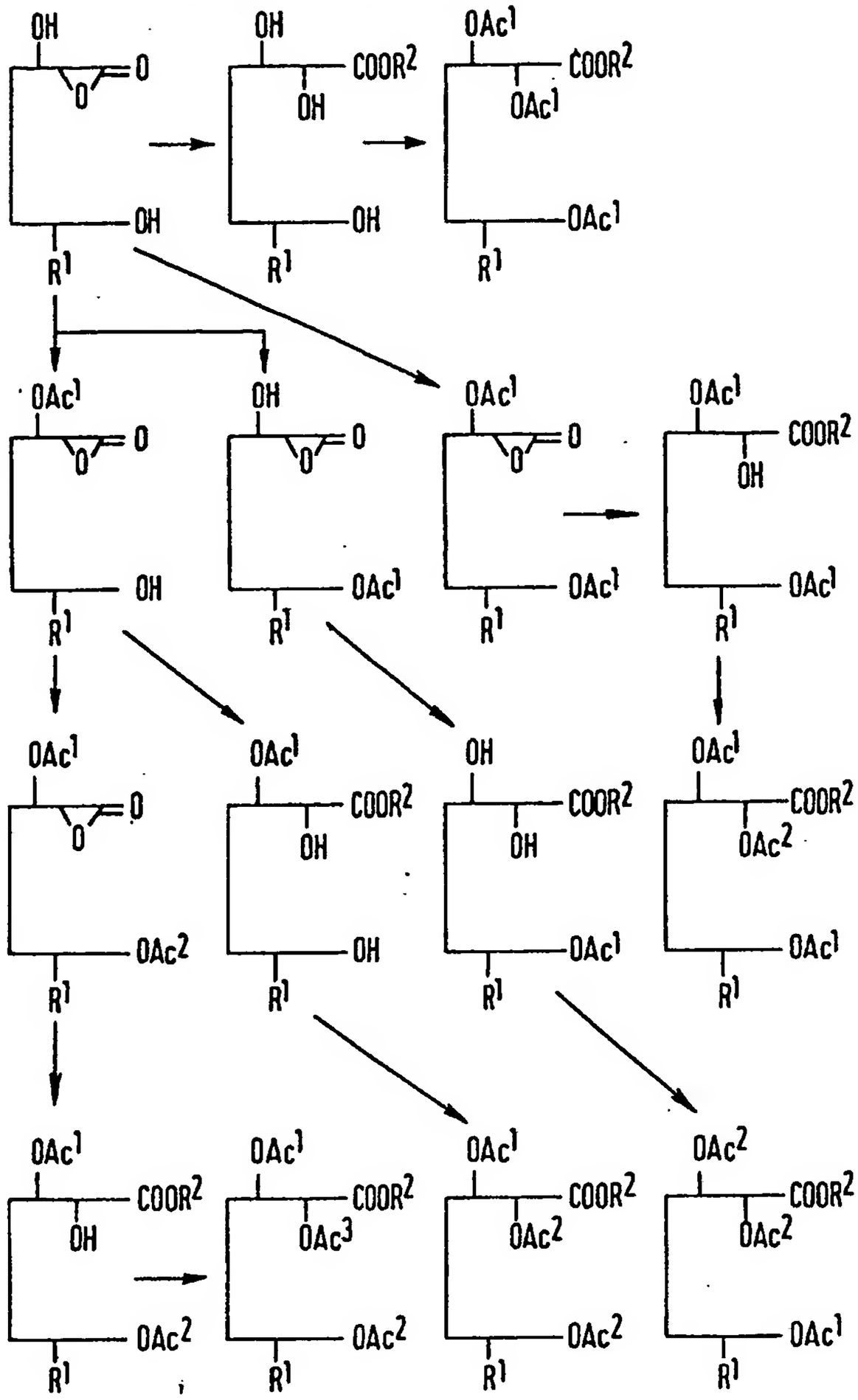
This reaction may be carried out under conventional conditions employing a free acid corresponding to the acyl group which it is desired to introduce in the presence of a condensing agent and, in this case, the compound of formula (XII) or (XVI) is simply contacted with the acid in the presence of the condensing agent. The condensing agent is preferably a dehydrating agent, for example a carbodiimide, such as dicyclohexylcarbodiimide. The reaction is normally carried out in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include dimethylformamide, dimethylacetamide, acetonitrile, pyridine, methylene chloride, chloroform and dioxan. The reaction may be carried out over a wide temperature range, but, in order to control side reactions, we normally prefer to conduct it at room temperature or with cooling; however, the reaction will also proceed at elevated temperatures. The time required for the reaction will vary depending upon the reaction temperature and the reagents employed, but the reaction will normally be complete within a period of from 1 to 20 hours. The desired compound may then be recovered from the reaction mixture by conventional means, for example by filtering off insolubles, diluting the filtrate with water, extracting the resulting mixture with a water-immiscible solvent and then distilling the solvent from the extract to give the desired product.

In the case of both of the above acylation reactions, where the starting material contains two or more free hydroxy groups, any of the mono, di or tri- acyl derivatives can be obtained by controlling the amount of acylating agent employed. If a mixture of these compounds is obtained, the separate compounds may be isolated using conventional isolation techniques, for example chromatography on silica gel.

The compounds of the invention may ultimately be prepared from the fermentation products ML-236A, ML-236B, Mb-530A and MB-530B or their corresponding carboxylic acids or carboxylic acid salts by any combination of the above reactions. These reactions are summarized in the following reaction scheme, in which the chemical structures of the compounds are simplified as follows:







In the above reaction scheme, Ac^1, Ac^2 and Ac^3 are the same or different and each represents an acyl group.

The compounds of the invention have been found to inhibit the activity of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), which is the rate- determining enzyme in the biosynthesis of cholesterol. According to the method of Knauss, *et al.* [J. Biol. Chem., *234*, 2835 (1959)], the inhibitory activities of the compounds of the invention against the biosynthesis of cholesterol, expressed as their ID_{50} values (i.e. the concentration required to inhibit the biosynthesis of cholesterol by 50%), varied from 1.0 to 0.03 μg/ml. Moreover, sodium salts, i.e. compounds of formula (I) in which R^2 represents a sodium atom, were found to be adsorbed during an *in vivo* test far better than the corresponding lactone and in general it is believed that the compounds of the invention have improved bioavailability compared with the corresponding lactones.

The compounds of the invention may be administered for the treatment of hypercholesterolaemia by any conventional means, but they are preferably administered in the form of tablets or capsules. The daily dose will vary depending upon the age, body weight and condition of the patient, but in general the compounds of the invention are preferably administered in an amount of from 1 mg to 10 mg per day, in a single dose or in divided doses.

The preparation of the compounds of the invention is further illustrated by the following Examples. Preparation of certain of the starting materials used in these Examples is illustrated by

Preparations 1—4 and other starting materials may be prepared in a manner similar to that described in these Preparations. The preparation of ML-236A and ML-236B are described in more detail in US Patent Specification No. 3,983,140 and the preparation of MB-530 (Monacolin K) is described in United Kingdom Patent Applications No. 2046737 and No. 2049664.

Preparation 1

3-*O*-Butyryl-ML-236A

918 mg of ML-236A were dissolved in 5 ml of pyridine, and 1 ml of butyric anhydride was added dropwise thereto at room temperature. After leaving the reaction mixture to stand overnight, it was diluted with water and extracted with diethyl ether. The extract was washed successively with water, a saturated aqueous solution of sodium bicarbonate, water, 1N hydrochloric acid and water and dried over anhydrous sodium sulphate. The solvent was distilled off from the solution and the residue was subjected to column chromatography through silica gel, eluted with a 5:1 by volume mixture of benzene and ethyl acetate, to give 930 mg of the desired product as a colourless oily substance.

Elemental analysis:

Calculated for $C_{22}H_{32}O_5$: C, 70.21%; H, 8.51%.
Found: C, 69.95%; H, 8.69%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
0.95 (3H, triplet);
4.27 (1H, multiplet);
5.32 (1H, multiplet).

Infrared Absorption Spectrum (liquid film) ν_{max} cm^{-1}:
3460, 1740.

Preparation 2

3,8′-Di(*O*-butyryl)-ML-236A

306 mg of ML-236A and 0.5 ml of pyridine were dissolved in 3 ml of methylene chloride, and 0.5 ml of butyryl chloride was added dropwise thereto, with ice-cooling. The mixture was stirred at room temperature for 1 hour and then washed adding water. The organic layer was separated and dried over anhydrous sodium sulphate, after which the solvent was distilled off. The resulting residue was subjected to column chromatography through silica gel, eluted with a 10:1 by volume mixture of benzene and ethyl acetate, to afford 384 mg of the desired product as a colourless oily substance.

Elemental analysis:

Calculated for $C_{26}H_{38}O_6$: C, 69.96%; H, 8.52%.
Found: C, 70.14%; H, 8.31%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
0.93 (6H, triplet);
5.2—5.5 (2H, multiplet).

Infrared Absorption Spectrum (liquid film) ν_{max} cm^{-1}:
1735, 1250, 1175.

Preparation 3

8′-*O*-Butyryl-ML-236A

918 mg of ML-236A and 0.36 ml of pyridine were dissolved in 10 ml of methylene chloride. The solution was cooled in an ice bath, and 0.35 ml of butyryl chloride was added dropwise thereto. After being stirred for 1 hour, the mixture was diluted with water. The organic layer was separated, washed with water and dried over anhydrous sodium sulphate. The solvent was distilled off and the residue was subjected to column chromatography through silica gel. The 3,8′-diacyl compound (described in Preparation 2) was obtained by eluting with a 10:1 by volume mixture of benzene and ethyl acetate, the 3-acyl compound (described in Preparation 1) was obtained by eluting with a 5:1 by volume mixture of benzene and ethyl acetate, and 395 mg of the desired product were obtained as colourless crystals melting at 124—5°C from the eluate using a 2:1 by volume mixture of benzene and ethyl acetate.

Elemental analysis:

Calculated for $C_{22}H_{32}O_5$: C, 70.21%; H, 8.51%.
Found: C, 70.25%; H, 8.50%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
0.95 (3H, triplet);
4.42 (1H, multiplet).

Infrared Absorption Spectrum (Nujol-trade mark) ν_{max} cm^{-1}:
3400, 1730, 1710.

Other acyl derivatives can be prepared by following the procedures described in these Preparations.

Preparation 4

Preparation of MB-530A

300 litres of a culture medium having a pH of 5.5 before sterilization and containing 5% w/v glucose, 0.5% w/v corn steep liquor, 2% w/v peptone (Kyokuto brand, available from Kyokuto Seiyaku KK, Japan) and 0.5% ammonium chloride were charged into a 600 litre fermenter and inoculated with a culture of *Monascus ruber* SANK 15177 (FERM 4956, NRRL 12081). Cultivation of the microorganism was continued for 120 hours at 27°C with an aeration rate of 300 litres/minute and agitation at 190 revolutions per minute.

At the end of this time, the culture broth was filtered in a filter press to give a filtrate and a filter cake comprising wet cells of the microorganism.

The filtrate was adjusted to a pH of 3.0 by the addition of 6N hydrochloric acid and then extracted with 400 litres of ethyl acetate. The extract (about 400 litres) was concentrated by evaporation under reduced pressure and then dehydrated over anhydrous sodium sulphate, after which it was evaporated to dryness, to give about 60 g of an oily product. This oily product was washed with ethylcyclohexane and with hexane and the residue (20 g) was separated by chromatography using a liquid chromatography device for large volume sampling (System 500 liquid chromatography, produced by Waters Co., U.S.A.), eluted with 60% v/v aqueous methanol. Fractions having a chromatographic retention time of 6 minutes were collected and concentrated by evaporation under reduced pressure to give 100 mg of the desired MB-530A as an oily product. This oily MB-530A was recrystallized from a mixture of acetone and diethyl ether to give 57 mg of the desired product in the form of colourless needles having the following properties:

1. Melting Point: 92—93°C.
2. Elemental Analysis:
   Calculated for $C_{19}H_{28}O_4$: C, 69.76%; H, 8.68%.
   Found: C, 71.22%; H, 8.81%.
3. Molecular weight: 320 (by mass analysis).
4. Molecular formula: $C_{19}H_{28}O_4$.
5. Ultraviolet Absorption Spectrum: As shown in Figure 1 of the accompanying drawings.
6. Infrared Absorption Spectrum: As shown in Figure 2 of the accompanying drawings.
7. Nuclear Magnetic Resonance Spectrum: As shown in Figure 3 of the accompanying drawings.
8. Solubility:
   readily soluble in methanol, ethanol, acetone and ethyl acetate;
   soluble in benzene;
   insoluble in hexane and petroleum ether.
9. Colouration reaction:
   a pink colour is seen when a thin layer chromatogram on silica gel of the compound is developed with 50% v/v sulphuric acid.
10. Inhibitory activity against the biosynthesis of cholesterol: a 50% inhibition of the synthesis of cholesterol in a rat liver is observed at a concentration of 0.04 μg/ml.

Example 1

Sodium ML-236A-carboxylate

0.4 g of ML-236A was added to 12 ml of 0.1N aqueous solution of sodium hydroxide, and the mixture was heated at 80—90°C for 2 hours. After completion of the reaction, insolubles were filtered off and the filtrate was lyophilized to afford 0.41 g of the desired product as a colourless powder.

Elemental analysis:
Calculated for $C_{18}H_{27}O_5Na$: C, 62.43%; H, 7.80%.
Found; C, 62.58%; H, 7.72%.

Example 2

Sodium 8′-*O*-butyryl-ML-236A-carboxylate

0.75 g of 8′-*O*-butyryl-ML-236A was added to 20 ml of a 0.1N aqueous solution of sodium hydroxide, and the resulting mixture was heated at 80—90°C for 2 hours. After completion of the reaction, insolubles were filtered off and the filtrate was lyophilized to give 0.83 g of the desired product as a colourless powder.

Elemental analysis:
Calculated for $C_{22}H_{33}O_6Na$: C, 63.46%; H, 7.93%; Na, 5.53%.
Found: C, 63.54%, H, 7.90%; Na, 5.50%.

Nuclear Magnetic Resonance Spectrum (D_2O) δ ppm:
0.95 (3H, triplet);
4.15 (2H, triplet);
3.5—4.5 (2H, multiplet).

Infrared Absorption Spectrum (Nujol) ν_{max} cm^{-1}:
3450, 1730, 1580.

Example 3

Sodium 8′-*O*-hexanoyl-ML-236A-carboxylate

0.88 g of 8′-*O*-hexanoyl-ML-236A was added to 20 ml of a 0.1N aqueous solution of sodium hydroxide. The mixture was treated in the same manner as described in Example 1, to give 0.84 g of the desired product as a colourless powder.

Elemental analysis:

Calculated for $C_{24}H_{37}O_6Na$: C, 64.86%; H, 8.33%; Na, 5.18%.
Found: C, 64.75%; H, 8.37%; Na, 5.25%.

Nuclear Magnetic Resonance Spectrum (D_2O) δ ppm:

0.87 (3H, triplet);
4.13 (2H, multiplet);
3.5—4.5 (2H, multiplet).

Infrared Absorption Spectrum (Nujol) ν_{max} cm^{-1}:

3450, 1730, 1580.

Example 4

Ethyl 8′-*O*-butyryl-ML-236A-carboxylate

0.79 g of 8′-*O*-butyryl-ML-236A were dissolved in 10 ml of ethanol, and 1 g of a sulphonic acid-type strongly acidic cation exchange resin (sold under the trade name Dowex 50W) was added thereto. The mixture was heated at 60—70°C for 3 hours. After completion of the reaction, the mixture was filtered and the filtrate was concentrated by evaporation under reduced pressure. The residue was purified by column chromatography through silica gel to afford 0.41 g of the desired product as a colourless oily substance.

Elemental analysis:

Calculated for $C_{24}H_{38}O_6$: C, 68.25%; H, 9.00%.
Found: C, 68.19%; H, 9.06%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.95 (3H, triplet);
1.23 (3H, triplet);
4.12 (2H, quartet);
3.5—4.5 (2H, multiplet).

Infrared Absorption Spectrum (liquid film) ν_{max} cm^{-1}:

3450, 1740.

Example 5

Ethyl 8′-*O*-hexanoyl-ML-236A-carboxylate

0.9 g of 8′-*O*-hexanoyl-ML-236A was dissolved in 10 ml of ethanol, and 1.5 g of a sulphonic acid-type strongly acidic cation exchange resin were added thereto. The mixture was treated in the same manner as described in Example 3, to give 0.55 g of the desired product as a colourless oily substance.

Elemental analysis:

Calculated for $C_{26}H_{46}O_6$: C, 69.33%; H, 9.33%.
Found: C, 69.21%; H, 9.39%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δppm:

0.87 (3H, triplet);
1.25 (3H, triplet);
4.13 (2H, quartet);
3.5—4.5 (2H, multiplet).

Infrared Absorption Spectrum (liquid film) ν_{max} cm^{-1}:

3400, 1730, 1720.

Example 6

Butyl 8′-*O*-butyryl-ML-236A-carboxylate

0.79 g of 8′-*O*-butyryl-ML-236A was dissolved in 10 ml of butanol, and 1.0 g of a sulphonic acid-type strongly acidic cation exchange resin was added thereto. The mixture was treated in the same manner as described in Example 3, to afford 0.59 g of the desired product as a colourless oily substance.

Elemental analysis:

Calculated for $C_{26}H_{42}O_6$: C, 69.33%; H, 9.33%.
Found: C, 69.25%; H, 9.40%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.95 (3H, triplet);
1.24 (3H, triplet);
4.12 (2H, triplet);
3.5—4.5 (2H, multiplet).

Infrared Absorption Spectrum (liquid film) ν_{max} cm^{-1}:

3440, 1730.

Example 7

Butyl 8′-*O*-(4-pentenoyl)-ML-236A-carboxylate

Following the procedure described in Example 3, but using 0.92 g of 8′-*O*-(4-pentenoyl)-ML-236A, 10 ml of butanol and 1.0 g of the ion exchange resin, there was obtained 0.45 g of the desired product as a colourless oily substance.

Elemental analysis:

Calculated for $C_{27}H_{42}O_6$: C, 70.13%; H, 9.09%.
Found: C, 70.04%; H, 9.13%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.24 (3H, multiplet);
3.5—4.5 (4H, multiplet);
4.8—6.2 (8H, multiplet);

Infrared Absorption Spectrum (liquid film) ν_{max} cm^{-1}:
3400, 1730.

Example 8

Butyl 8′-*O*-isovaleryl-MB-530A-carboxylate

Following the procedure described in Example 3, but using 0.9 g of 8′-*O*-isovaleryl-MB-530A, 10 ml of butanol and 1.0 g of the ion exchange resin, there was obtained 0.52 g of the desired product as a colourless oily substance.

Elemental analysis:

Calculated for $C_{27}H_{44}O_6$: C, 69.83%; H, 9.48%.
Found: C, 69.77%; H, 9.46%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
0.89 (1H, doublet);
1.24 (3H, triplet);
4.12 (2H, triplet);
3.5—4.5 (2H, multiplet).

Infrared Absorption Spectrum (liquid film) ν_{max} cm^{-1}:
3430, 1730.

Example 9

Benzyl 8′-*O*-butyryl-ML-236A-carboxylate

1.0 g of sodium 8′-*O*-butyryl-ML-236A-carboxylate was dissolved in 5 ml of dimethylformamide, and 1 ml of benzyl chloride was added thereto. The mixture was left to stand overnight. The reaction mixture was then diluted with water and extracted with ethyl acetate. The organic layer was separated, washed with water and dried over anhydrous sodium sulphate. The solvent was distilled off under reduced pressure and the residue was purified by column chromatography through silica gel, to afford 1.2 g of the desired product as a colourless oily substance.

Elemental analysis:

Calculated for $C_{29}H_{40}O_6$: C, 71.90%; H, 8.26%.
Found: C, 71.84%, H, 8.25%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
0.94 (3H, triplet);
1.24 (3H, triplet);
4.11 (2H, triplet);
3.5—4.5 (2H, multiplet);
5.20 (2H, singlet);
7.42 (5H, singlet).

Infrared Absorption Spectrum (liquid film) ν_{max} cm^{-1}:
3540, 1730.

Example 10

Benzyl 8′-*O*-hexanoyl-ML-236A-carboxylate

Following the procedure described in Example 8, but using 1.2 g of sodium 8′-*O*-hexanoyl-ML-236A-carboxylate and 1 ml of benzyl chloride, there were obtained 1.3 g of the desired product as a colourless oily substance.

Elemental analysis:

Calculated for $C_{31}H_{44}O_6$: C, 72.66%; H, 8.59%.
Found: C, 72.58%; H, 8.50%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
0.89 (3H, triplet);
4.14 (2H, triplet);
3.5—4.5 (2H, multiplet);

5.21 (2H, singlet);
7.44 (5H, singlet).
Infrared Absorption Spectrum (liquid film) ν_{max} cm^{-1}:
3400, 1730.

Example 11
Phenacyl 8′-*O*-butyryl-MB-530A-carboxylate

Following the procedure described in Example 8, but using 0.86 g of sodium 8′-*O*-butyryl-MB-530A-carboxylate and 0.45 g of phenacyl bromide, there was obtained 1.0 g of the desired product as a colourless oily substance.

Elemental analysis:
Calculated for $C_{31}H_{42}O_7$: C, 70.72%; H, 7.98%.
Found: C, 70.65%; H, 8.04%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
0.95 (3H, triplet);
4.13 (2H, triplet);
3.5—4.5 (2H, multiplet);
5.44 (2H, singlet);
7.4—8.2 (5H, multiplet).
Infrared Absorption Spectrum (liquid film) ν_{max} cm^{-1}:
3450, 1730, 1700.

Example 12
Butyl 3,5-di(*O*-acetyl)-ML-236B-carboxylate

0.32 g of butyl ML-236B-carboxylate was dissolved in 1 ml of pyridine. After the addition of 1 ml of acetic anhydride, the mixture was left to stand at room temperature for 1 hour. The reaction mixture was then diluted with water and extracted with ethyl acetate. The solvent was distilled under reduced pressure from the extract and the residue was purified by column chromatography through silica gel, to afford 0.35 g of the desired product as a colourless oily substance.

Elemental analysis:
Calculated for $C_{31}H_{48}O_8$: C, 67.88%; H, 8.76%.
Found: C, 67.74%; H, 8.81%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
2.00 (3H, singlet);
2.03 (3H, singlet).
Infrared Absorption Spectrum (liquid film) ν_{max} cm^{-1}:
1740.

Example 13
Butyl 3,5-di(*O*-benzoyl-ML-236B-carboxylate

Following the procedure described in Example 11, but using 0.34 g of butyl ML-236B-carboxylate, 0.3 ml of benzoyl chloride and 1 ml of pyridine, there was obtained 0.38 g of the desired product as a colourless oily substance.

Elemental analysis:
Calculated for $C_{41}H_{52}O_8$: C, 73.21%; H, 7.74%.
Found: C, 73.10%; H, 7.89%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
7.2—7.6 (3H, multiplet);
7.8—8.2 (2H, multiplet).
Infrared Absorption Spectrum (liquid film) ν_{max} cm^{-1}:
1720.

Example 14
Sodium ML-236A-carboxylate

300 litres of a culture medium (pH 5.5 before sterilization) containing 2% w/v glucose, 0.1% w/v peptone ("Kyokuto" brand) and 3% w/v malt extract were charged into a 600 litre fermenter and inoculated with the organism *Penicillium citrinum* SANK 18767. Cultivation was continued at 26°C for 96 hours under aerobic conditions at an aeration rate of 300 litres per minute and agitation at 145 rotations per minute. The culture broth (containing the organism) was adjusted to pH 3.4 with 6N hydrochloric acid and extracted with 800 litres of ethyl acetate. The extract was washed with 200 litres of a saturated aqueous solution of sodium chloride and then concentrated by evaporation in a vacuum to 18 litres. The resulting solution was extracted with 600 litres of ethyl acetate. 50 g of trifluoroacetic acid were added to the extract and reacted at 80°C for 30 minutes. The reaction mixture was washed successively with 20 litres of a 2% w/v aqueous solution of sodium bicarbonate and 2C litres of a 10% w/v aqueous solution of sodium chloride, after which it was concentrated by

evaporation under reduced pressure, to give 130 g of an oily substance. This oil was dissolved in 400 ml of methanol. 20 ml of the methanolic solution (containing 6.5 g of the oil) were subjected to preparative rapid liquid chromatography, System 500 type (produced by Waters Co., Ltd.) equipped with a Prepac C_{18} column (reversed phase column). A mixture of methanol and water (60:40 v/v) was used as the developer. The development was carried out at a flow rate of 200 ml/minute (developing time: about 10 minutes), watching a differential refractometer connected to the apparatus, the portion showing a main peak on the differential refractometer was separated. This operation was repeated and resulting main peak fractions were collected and concentrated to give 9.2 g of an oily substance, which was dissolved in 30 ml of methanol. 6 ml of the methanolic solution (containing about 1.8 g of the oil) were subjected again to the same chromatography but developed with a 55:45 v/v mixture of methanol and water at a flow rate of 200 ml/minute. A portion showing a main peak was separated. This operation was repeated and the main peak fractions were collected and concentrated to afford 1020 mg of ML-236A as an oily substance. To this substance were added 33.2 ml of 0.1N aqueous solution of sodium hydroxide and the mixture was stirred at 50—60°C for 3 hours. Insolubles were filtered off and the filtrate was lyophilized, to give 1090 mg of sodium ML-236A-carboxylate.

Example 15

Sodium ML-236A-carboxylate

1030 litres of an ethyl acetate extract from the culture broth obtained by the same procedures as described in Example 14 were washed with 200 litres of a saturated aqueous solution of sodium chloride. The extract was then dried over anhydrous sodium sulphate and concentrated to dryness to give 120 g of an oily substance containing ML-236A carboxylic acid.

To this oil was added methanol to give a total volume of 200 ml. 20 ml of the solution was subjected to preparative rapid liquid chromatography equipped with a reversed phase column (the same as used in Example 14) and eluted with a 20% v/v aqueous methanol solution (containing 2% acetic acid) at a flow rate of 200 ml/minute. A portion showing a main peak on the differential refractometer was separated (7—10 minutes). The remaining 120 ml were treated by the same procedure. The resulting main peak fractions were collected, concentrated and extracted with ethyl acetate. The filtrate was concentrated to dryness after adding heptane, to give 8.7 g of an oily substance, which was dissolved in 20 ml of methanol and subjected to chromatography under the same conditions as above to give 930 mg of ML-236A carboxylic acid. To this product were added 2 ml of methanol and 100 ml of water and the resulting solution was adjusted to pH 8.0 with 1N aqueous sodium hydroxide to produce a clear aqueous solution, which was then lyophilized to give 980 mg of sodium ML-236A-carboxylate as a white powder.

Example 16

Sodium MB-530A-carboxylate

300 litres of a culture medium (pH 5.5 before sterilization) containing 5% w/v glucose, 0.5% w/v corn steep liquor, 2% w/v peptone ("Kyokuto" brand) and 0.5% w/v ammonium chloride were charged into a 600 litre fermenter and inoculated with the organism *Monascus ruber* SANK 18174. Cultivation was continued at 26°C for 116 hours under aerobic conditions at an aeration rate of 300 litres per minute and agitation at 190 rotations per minute. The culture broth (containing the organism) was adjusted to pH 3.4 with 6N hydrochloric acid and extracted with 800 litres of ethyl acetate. The extract was washed with 200 litres of a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulphate. It was then concentrated to 18 litres by evaporation under reduced pressure. The resulting solution was extracted with 600 litres of ethyl acetate. 50 g of trifluoroacetic acid were added to the extract and reacted at 80°C for 30 minutes. The reaction mixture was washed successively with 10 litres of a 2% w/v aqueous solution of sodium bicarbonate and 10 litres of a 10% w/v aqueous solution of sodium chloride, and then was concentrated to give 105 g of an oily substance. This oil was dissolved in 400 ml of methanol. 20 ml of the methanolic solution (containing about 5.3 g of the oil) were subjected to preparative rapid liquid chromatography with a reverse phase column (the same as in Example 14). A 65:35 v/v mixture of methanol and water was used as the developer. The development was carried out at a flow rate of 200 ml/minute (developing time: about 15 minutes), watching a differential refractometer connected to the apparatus, the portion showing a main peak on the differential refractometer was separated. This operation was repeated and the resulting main peak fractions were collected and concentrated to give 7.9 g of an oily substance, which was dissolved in 30 ml of methanol. 60 ml of this methanolic solution (containing about 1.6 g of the oil) were subjected again to the same chromatography but developed with a 60:40 v/v mixture of methanol and water at a flow rate of 200 ml/minute. A portion showing a main peak was separated. This operation was repeated and the main peak fractions were collected and concentrated. There were obtained 679 mg of MB-530A as an oily substance. To this substance were added 21 ml of a 0.1N aqueous solution of sodium hydroxide and the mixture was stirred at 50—60°C for 3 hours. Insolubles were filtered off and the filtrate was lyophilized to give 720 mg of sodium MB-530A-carboxylate.

Elemental analysis:

calculated for $C_{19}H_{29}O_5Na$: C, 63.33%; H, 8.06%.

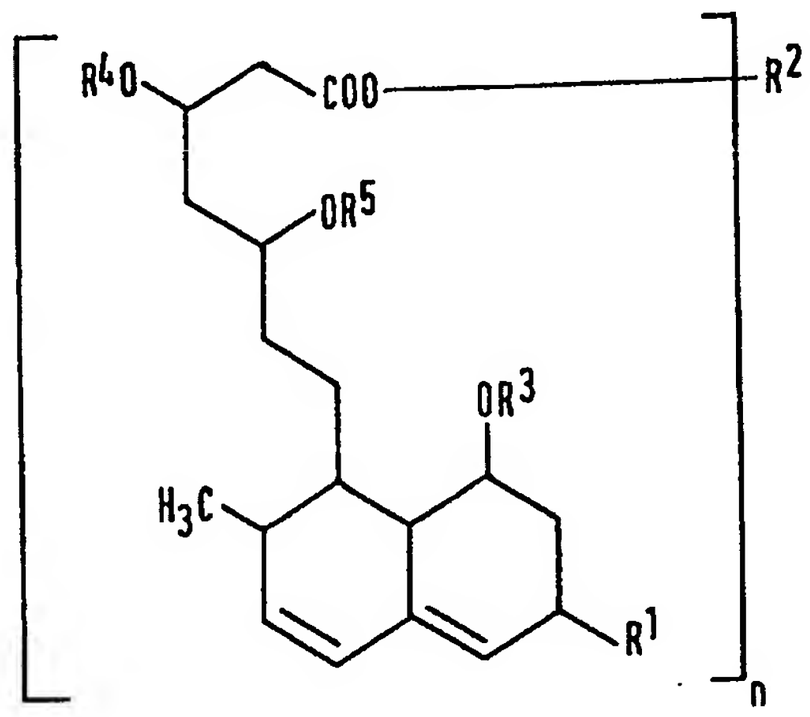
Found: C, 63.51%; H, 7.97%.

Example 17
Sodium MB-530A-carboxylate

300 litres of a culture medium (pH 7.4 before sterilization) containing 1.5% w/v soluble starch, 1.5% w/v glycerine, 2% w/v fish meal and 0.2% w/v calcium carbonate were charged into a 600 litre fermenter and inoculated with the organism *Monascus ruber* SANK 17075 (CBS 832.70). Cultivation was continued at a temperature of 26°C for 120 hours under aerobic conditions at an aeration rate of 300 litres per minute and agitation at 190 rotations per minute. The resulting culture broth was filtered using a filter press to give 35 kg of the wet organism, to which 100 litres of water were added. The mixture was adjusted to pH 12 with sodium hydroxide, with stirring, and left to stand at room temperature for 1 hour. 2 kg of Hyflo Super Cel filter aid were added to the mixture, which was filtered by a filter press. The filtrate was adjusted to pH 10 with hydrochloric acid and adsorbed on a column charged with 5 litres of HP-20 resin. It was then washed with 15 litres each of water and 10% v/v aqueous methanol, after which it was eluted with 60% v/v aqueous methanol. The eluate was concentrated to a volume of about 10 litres. The residue was adjusted to pH 2 with hydrochloric acid and extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulphate and concentrated to dryness to give 20 g of an oily substance containing MB-530A carboxylic acid. To this oil was added methanol to a total volume of 100 ml. 20 ml of the solution were subjected to preparative rapid liquid chromatography equipped with a reversed phase column (the same as used in Example 14) and eluted with a 13% v/v aqueous methanol solution (containing 2% acetic acid) at a flow rate of 200 ml/minute. A portion showing a main peak on the differential refractometer was separated (7—10 minutes). The remaining 80 ml were treated in the same manner. The resulting main peak fractions were collected, concentrated and extracted with ethyl acetate. The extract was concentrated to dryness after adding heptane, to give 920 mg of an oily substance, which was dissolved in 20 ml of methanol and subjected to chromatography under the same conditions as above to give 120 mg of MB-530A carboxylic acid. To this product were added 2 ml of methanol and 100 ml of water and the resulting solution was adjusted to pH 8.0 with 1N aqueous sodium hydroxide to produce a clear aqueous solution. This was lyophilized to give 110 mg of sodium MB-530A-carboxylate as a white powder.

Claims

1. Compounds of formula (I):



(I)

wherein:

R^1 represents a hydrogen atom or a methyl group;

R^2 represents a hydrogen atom, the alcoholic moiety of an ester of the cationic moiety of a salt; and

R^3, R^4 and R^5 are the same or different and each represents a hydrogen atom or an organic or inorganic acyl group, provided that, when R^3 represents a 2-methylbutyryl group, R^4 and R^5 both represent acyl groups.

2. Compounds as claimed in Claim 1, in which:

R^1 represents a hydrogen atom or a methyl group;

R^2 represents a hydrogen atom, a metal atom, an ammonium group, an alkyl-substituted ammonium group, a group capable of forming a salt derived from a basic amino acid, an alkyl group, an aralkyl group optionally having a substituent on the aryl moiety or a phenacyl group optionally having a substituent on the phenyl moiety, said substituents being selected from C_1—C_4 alkyl groups, C_1—C_4 alkoxy groups, halogen atoms and trifluoromethyl groups; and

R^3, R^4 and R^5 are the same or different and each represents a hydrogen atom, an aliphatic acyl

group, an aromatic acyl group or an araliphatic acyl group, provided that, when R^3 represents a 2-methylbutyryl group, R^4 and R^5 both represent acyl groups.

3. Compounds as claimed in Claim 1, in which:

R^1 represents a hydrogen atom or a methyl group;

R^2 represents a hydrogen atom, an alkali metal atom, an alkaline earth metal atom, aluminium, zinc, iron, germanium, an ammonium group, a group capable of forming a salt derived from a basic amino acid, a C_1—C_8 alkyl group, an aralkyl group optionally having a substituent on the aryl moiety, or a phenacyl group optionally having a substituent on the phenyl moiety, said substituent being selected from C_1—C_4 alkyl groups, C_1—C_4 alkoxy groups, halogen atoms, and trifluoromethyl groups; and

R^3, R^4 and R^5 are the same or different and each represents a hydrogen atom, a C_2—C_{20} alkanoyl group, a C_3—C_{20} alkenoyl group, a C_3—C_{20} alkynoyl group, a C_7—C_{15} aromatic acyl group, a C_8—C_9 aralkanoyl group or a C_9 aralkenoyl group, provided that, when R^3 represents a 2-methylbutyryl group, R^4 and R^5 both represent acyl groups.

4. Compounds as claimed in Claim 1, in which:

R^1 represents a hydrogen atom or a methyl group;

R^2 represents a hydrogen atom, an alkali metal atom, an alkaline earth metal atom, an ammonium group, a group capable of forming a salt derived from a basic amino acid, a C_1—C_4 alkyl group, a benzyl group or a phenacyl group; and

R^3, R^4 and R^5 are the same or different and each represents a hydrogen atom, a C_2—C_6 alkanoyl group, a C_3—C_6 alkenoyl group or a benzoyl group, provided that, when R^3 represents a 2-methylbutyryl group, R^4 and R^5 both represent acyl groups.

5. Compounds as claimed in Claim 1, in which:

R^1 represents a hydrogen atom or a methyl group;

R^2 represents a C_1—C_4 alkyl group, a benzyl group or a phenacyl group;

R^3 represents a C_2—C_6 alkanoyl group or a C_3—C_6 alkenoyl group; and

R^4 and R^5 are the same or different and each represents a C_2—C_6 alkanoyl group or a benzoyl group.

6. Compounds as claimed in Claim 1, in which:

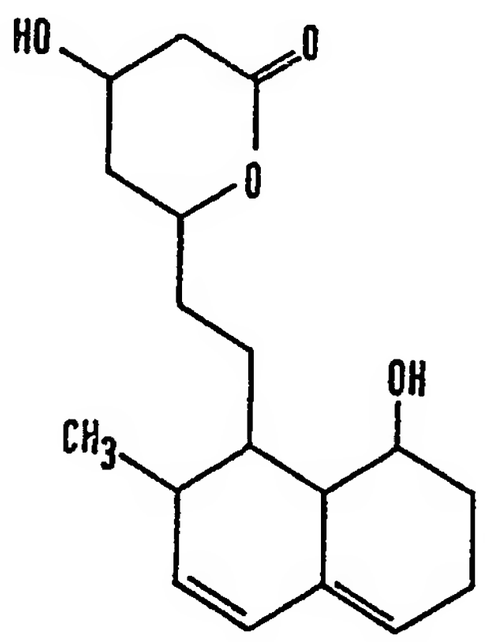
R^1 represents a hydrogen atom;

R^2 represents a C_1—C_4 alkyl group;

R^3 represents a C_2—C_6 alkanoyl group; and

R^4 and R^5 are the same or different and each represents an acetyl group or a benzoyl group.

7. Compounds of formula (II):



(II)

wherein:

R^1 represents a hydrogen atom or a methyl group;

R^{2a} represents a hydrogen atom, an alkali metal atom, an alkaline earth metal atom, an ammonium group, a group capable of forming a salt derived from a basic amino acid, a C_1—C_4 alkyl group, a benzyl group or a phenacyl group;

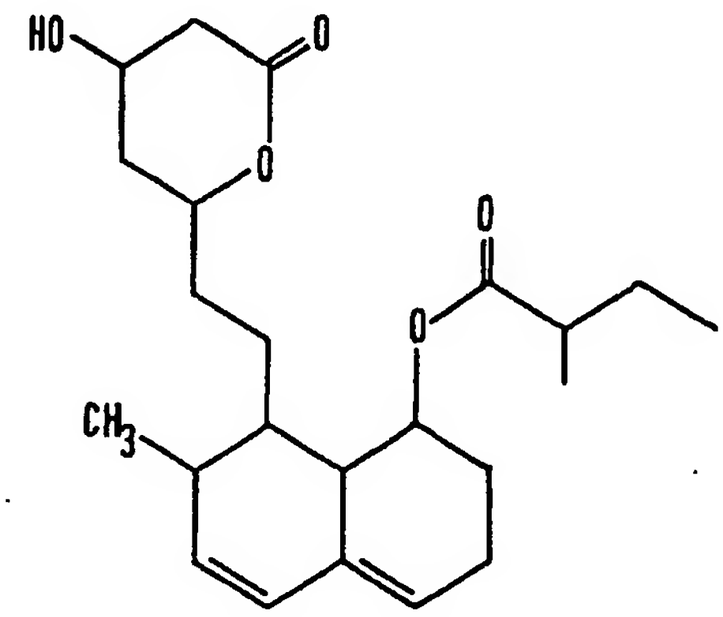
R^{3a} represents a C_2—C_6 alkanoyl group other than a 2-methylbutyryl group or a C_3—C_6 alkenoyl group; and

m represents the valence of R^{2a}.

8. Compounds as claimed in Claim 7, in which R^{2a} represents a C_1—C_4 alkyl group, a benzyl group or a phenacyl group.

9. Compounds as claimed in Claim 7, in which R^{2a} represents an alkali metal atom.

10. Compounds of formula (III):



(III)

wherein:

R^1 represents a hydrogen atom or a methyl group; and

M represents a hydrogen atom or an alkali metal atom.

11. Compounds as claimed in Claim 10, in which M represents an alkali metal atom.

12. Compounds as claimed in Claim 10, in which M represents a sodium atom.

13. Sodium ML-236A-carboxylate.

14. Sodium MB-530A-carboxylate.

15. Sodium 8′-*O*-butyryl-ML-236A-carboxylate.

16. Sodium 8′-*O*-hexanoyl-ML-236A-carboxylate.

17. Ethyl 8′-*O*-butyryl-ML-236A-carboxylate.

18. Ethyl 8′-*O*-hexanoyl-ML-236A-carboxylate.

19. Butyl 8′-*O*-butyryl-ML-236A-carboxylate.

20. Butyl 8′-*O*-(4-pentenoyl)-ML-236A-carboxylate.

21. Butyl 8′-*O*-isovaleryl-MB-530A-carboxylate.

22. Benzyl 8′-*O*-butyryl-MB-236A-carboxylate.

23. Benzyl 8′-*O*-hexanoyl-ML-236A-carboxylate.

24. Phenacyl 8′-*O*-butyryl-MB-530A-carboxylate.

25. Butyl 3,5-di(*O*-acetyl)-ML-236B-carboxylate.

26. Butyl 3,5-di(*O*-benzoyl)-ML-236B-carboxylate.

27. A process for producing an ML-236A carboxylic acid salt in which an ML-236A-producing microorganism of the genus *Penicillium* is cultivated in a culture medium therefor and the ML-236A carboxylic acid salt is recovered from the resulting culture broth.

28. A process as claimed in Claim 27, in which said microorganism is a strain of *Penicillium citrinum, Penicillium chrysogenum* or *Penicillium notatum*.

29. A process as claimed in Claim 28, in which said microorganism is *Penicillium citrinum* SANK 18767 (FERM 2609), *Penicillium citrinum* SANK 24467, *Penicillium citrinum* SANK 24567, *Penicillium chrysogenum* SANK 12768 (ATCC 100020) or *Penicillium notatum* SANK 24867.

30. A process as claimed in any one of Claims 27 to 29, in which said salt is an alkali metal salt.

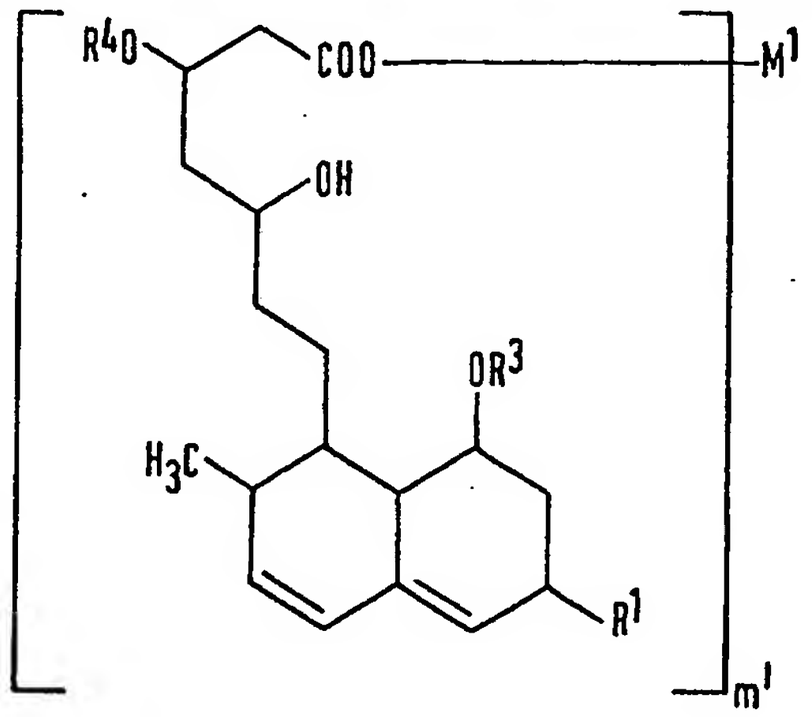
31. A process for producing an MB-530A carboxylic acid salt in which an MB-530A- producing microorganism of the genus *Monascus* is cultivated in a culture medium therefor and the MB-530A carboxylic acid salt is recovered from the resulting culture broth.

32. A process as claimed in Claim 31, in which said microorganism is a strain of *Monascus ruber, Monascus anka, Monascus paxii, Monascus purpureus* or *Monascus vitreus*.

33. A process as claimed in Claim 32, in which said microorganism is *Monascus ruber* SANK 11272 (IFO 9203), *Monascus ruber* SANK 17075 (CBS 832.70), *Monascus ruber* SANK 17175 (CBS 503.70), *Monascus ruber* SANK 17275 (ATCC 18199), *Monascus ruber* SANK 15177 (FERM 4956), *Monascus ruber* SANK 13778 (FERM 4959), *Monascus ruber* SANK 10671 (FERM 4958), *Monascus ruber* SANK 18174 (FERM 4957), *Monascus anka* SANK 10171 (IFO 6540), *Monascus paxii* SANK 11172 (IFO 8201), *Monascus purpureus* SANK 10271 (IFO 4513) or *Monascus vitreus* SANK 10960 (NIHS 609, e-609; FERM 4960).

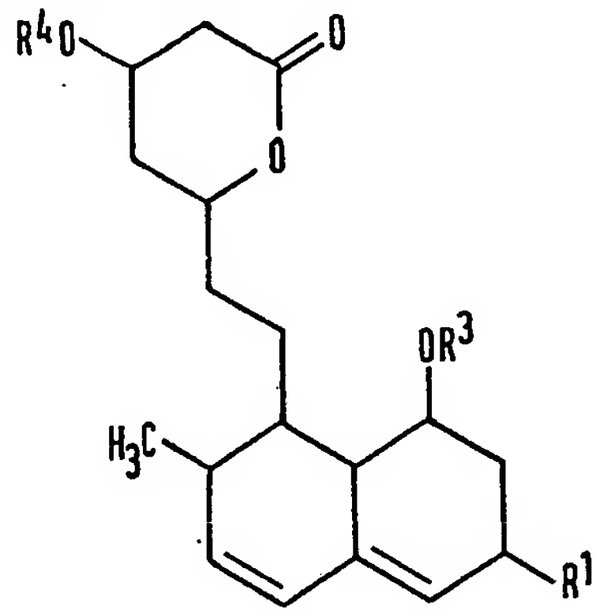
34. A process as claimed in any one of Claims 31 to 33, in which said salt is an alkali metal salt.

35. A process for preparing a carboxylic acid salt of formula (IV):



(IV)

(wherein:
R^1 represents a hydrogen atom or a methyl group;
R^3 and R^4 are the same or different and each represents a hydrogen atom or an acyl group, provided that, when R^3 represents a 2-methylbutyryl group, R^4 represents an acyl group;
M^1 represents the cationic moiety of a salt; and
m' is the valence of M^1),
in which a lactone compound of formula (V):



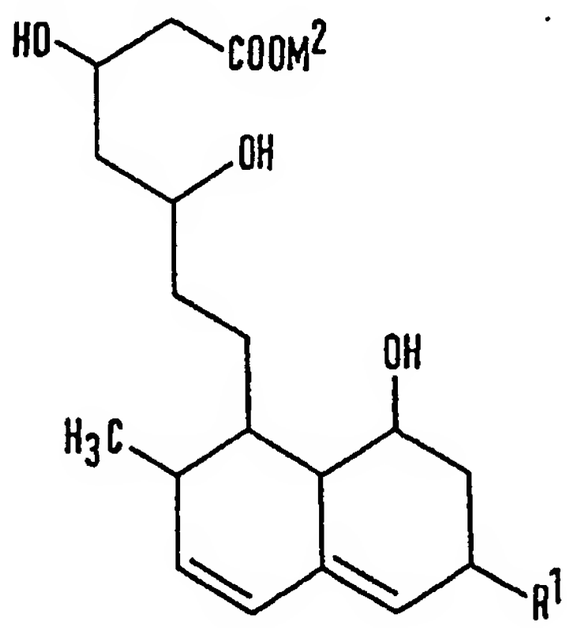
(V)

(wherein R^1, R^3, R^4, M^1 and m' are as defined above) is hydrolyzed and, if desired, the carboxy group of the product thus obtained is converted to the corresponding salt.

36. A process as claimed in Claim 35, in which said hydrolysis is effected in an alkali solution and M^1 represents an alkali metal atom.

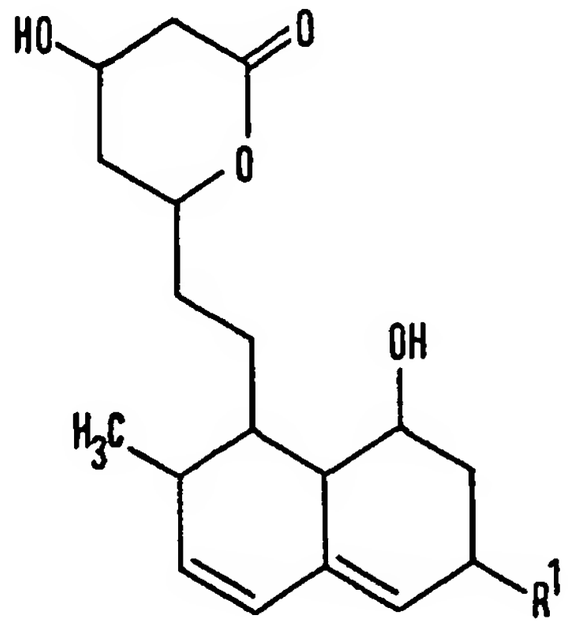
37. A process as claimed in Claim 35 or Claim 36, in which:
R^1 represents a hydrogen atom or a methyl group;
R^3 represents a hydrogen atom, a C_2—C_6 alkanoyl group or a C_3—C_6 alkenoyl group; and
R^4 represents a hydrogen atom, a C_2—C_6 alkanoyl group or a benzoyl group.

38. A process for preparing a carboxylic acid derivative of formula (VI):



(VI)

(wherein R^1 represents a hydrogen atom or a methyl group and M^2 represents an alkali metal atom) in which a compound of formula (VII):

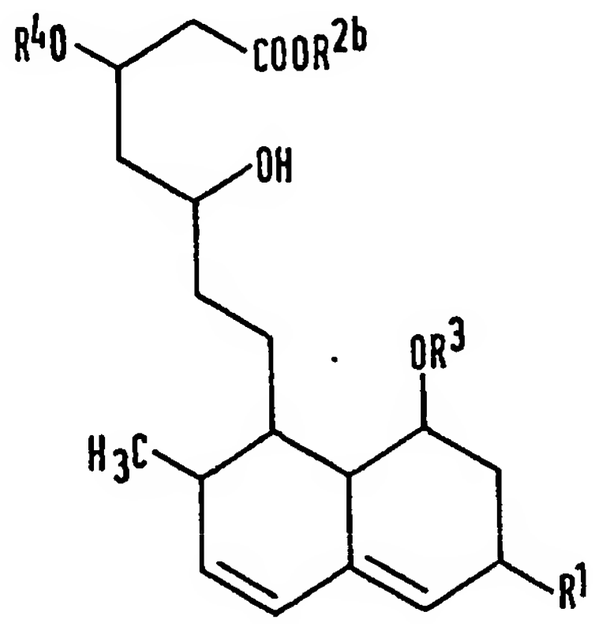


(VII)

(wherein R^1 is as defined above) is hydrolyzed in an alkali solution.

39. A process as claimed in Claim 38, in which M^2 represents a sodium atom and said alkali solution is an aqueous solution of sodium hydroxide.

40. A process for preparing a carboxylic acid ester of formula (VIII):



(VIII)

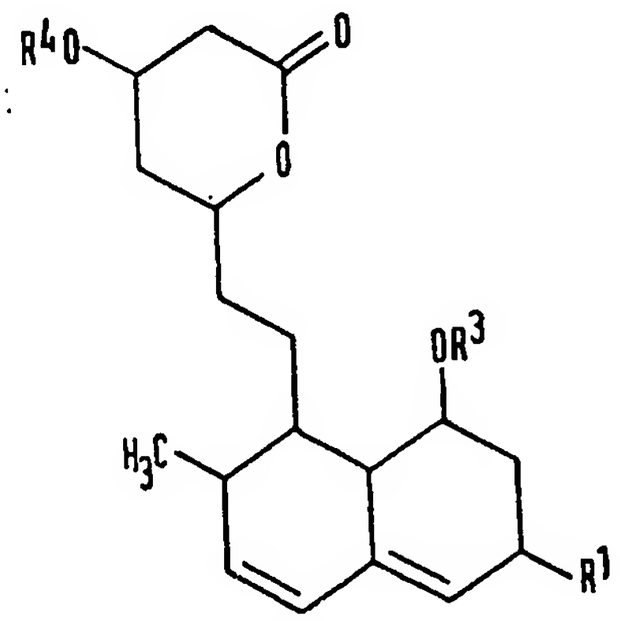
(wherein:

R^1 represents a hydrogen atom or a methyl group;

R^3 and R^4 are the same or different and each represents a hydrogen atom or an acyl group, provided that, when R^3 represents a 2-methylbutyryl group, R^4 represents an acyl group; and

R^{2b} represents an alkyl group or an aralkyl group),

in which a lactone compound of formula (V):



(V)

(wherein R^1, R^3 and R^4 are as defined above) is reacted with an alcohol in the presence of an acid catalyst.

41. A process as claimed in Claim 40, in which said acid catalyst is an inorganic acid, a Lewis acid or a cation exchange resin.

42. A process as claimed in Claim 41, in which said acid catalyst is a strongly acidic cation exchange resin.

43. A process as claimed in any one of Claims 40 to 42, in which:

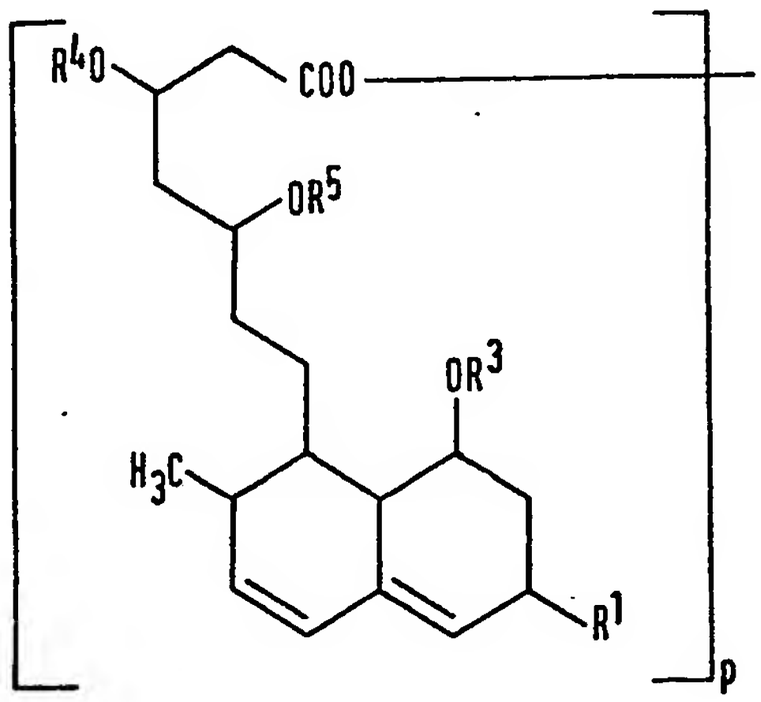
R^1 represents a hydrogen atom or a methyl group;

R^3 represents a hydrogen atom, a C_2—C_6 alkanoyl group or a C_3—C_6 alkenoyl group;

R^4 represents a hydrogen atom, a C_2—C_6 alkanoyl group or a benzoyl group (provided that, when R^3 represents a 2-methylbutyryl group, R^4 represents an acyl group); and

said alcohol is a C_1—C_4 alkanol.

44. A process for preparing a carboxylic acid ester of formula (IX):



(IX)

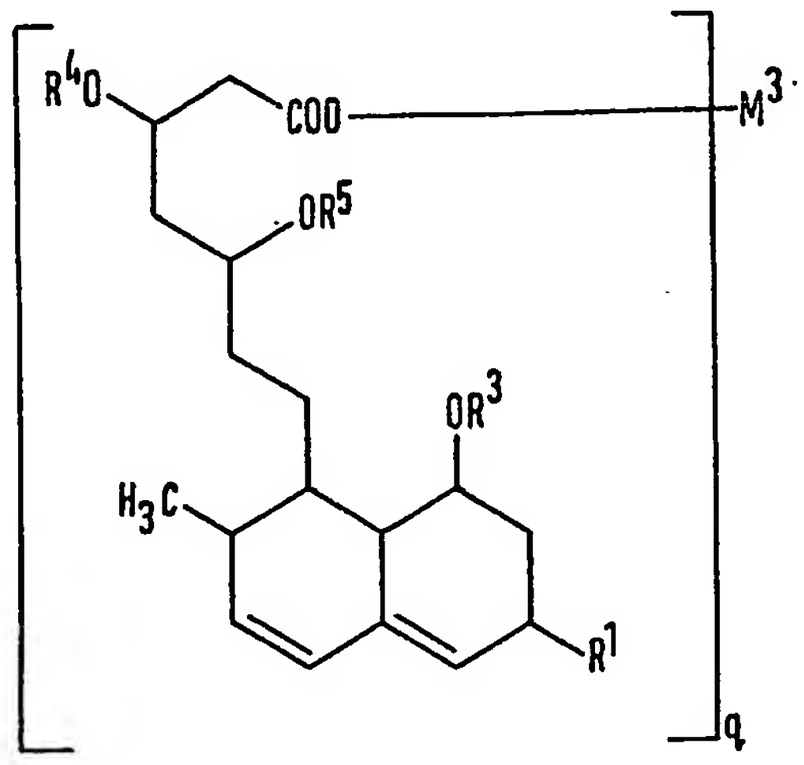
(wherein:

R^1, R^3, R^4 and R^5 are as defined in Claim 1;

R^{2c} represents the alcoholic moiety of an ester; and

p is the valence of R^{2c}),

in which a carboxylic acid salt of formula (X):



(X)

(wherein R^1, R^3, R^4 and R^5 are as defined above, M^3 represents an alkali or alkaline earth metal atom, and *q* is the valence of M^3) is reacted with an esterifying agent.

45. A process as claimed in Claim 44, in which said esterifying agent is an alkyl halide, an aralkyl halide or a phenacyl halide.

46. A process as claimed in Claim 44 or Claim 45, in which M^3 represents an alkali metal atom.

47. A process as claimed in Claim 46, in which said salt (X) in which M^3 represents an alkali metal atom is formed *in situ* prior to said reaction with an esterifying agent.

48. A process as claimed in any one of Claims 44 to 47, in which:

R^1 represents a hydrogen atom or a methyl group;

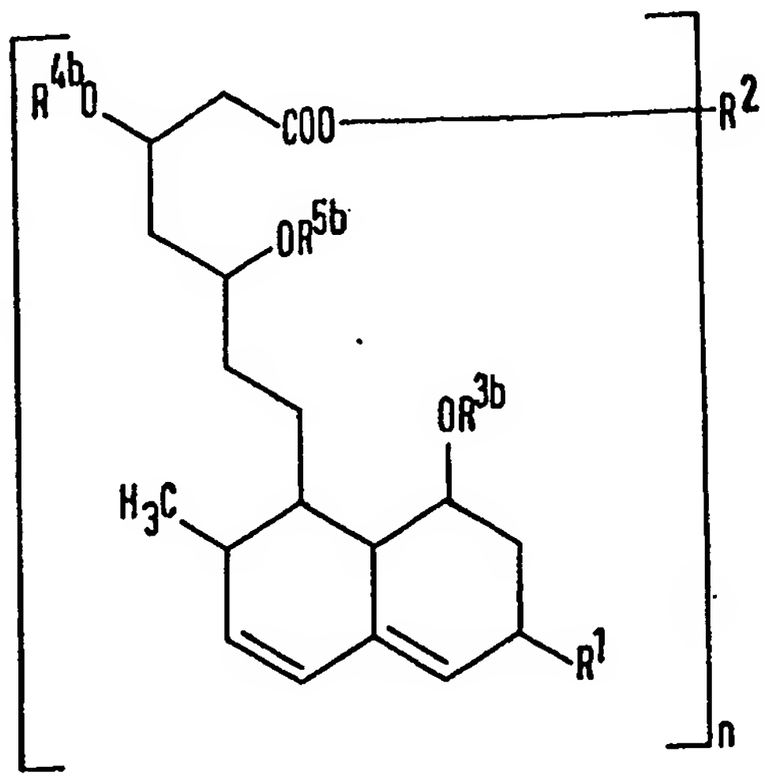
R^3 represents a hydrogen atom, a C_2—C_6 alkanoyl group or a C_3—C_6 alkenoyl group;

R^4 and R^5 are the same or different and each represents a hydrogen atom, a C_2—C_8 alkanoyl group or a benzoyl group, provided that, when R^3 represents a 2-methylbutyryl group, R^4 and R^5 both represent acyl groups;

M^3 represents an alkali metal atom; and

said esterifying agent is a benzyl halide or a phenacyl halide.

49. A process for preparing a triacyl compound of formula (XI):



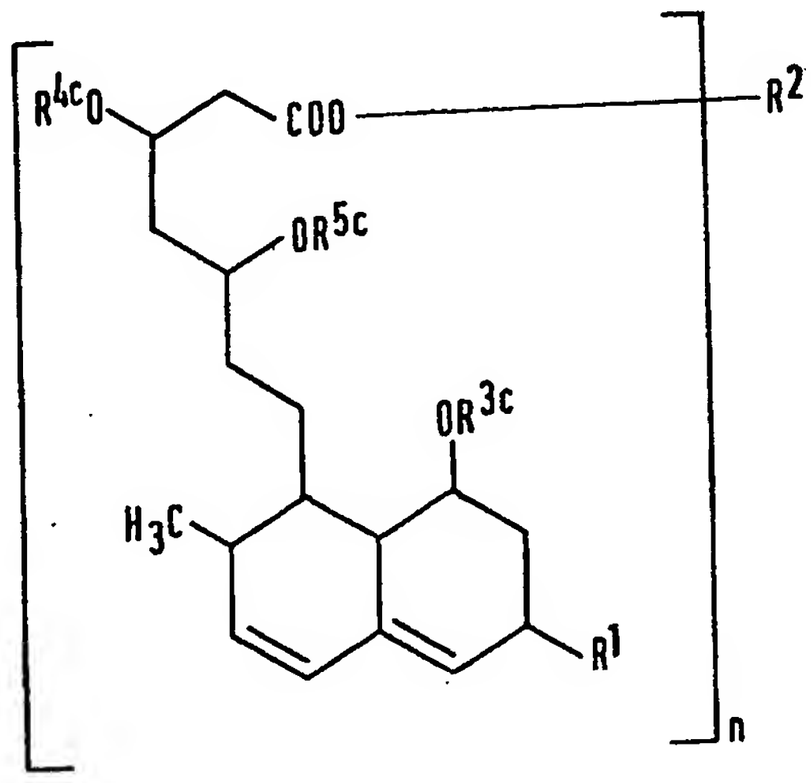
(XI)

(wherein:

R^1, R^2 and n are as defined in Claim 1; and

R^{3b}, R^{4b} and R^{5b} are the same or different and each represents an acyl group),

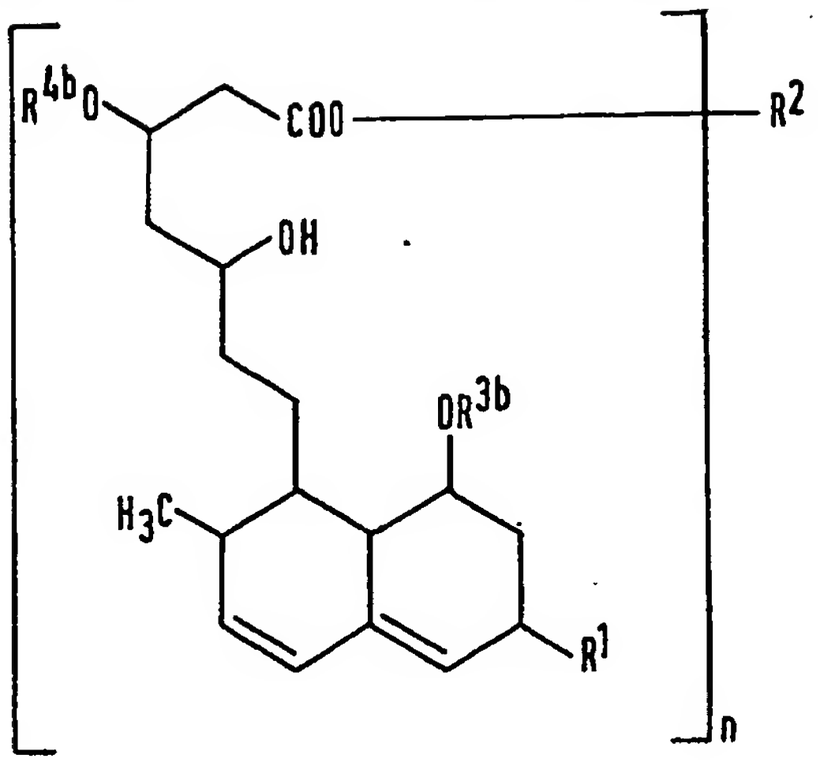
in which a compound of formula (XII):



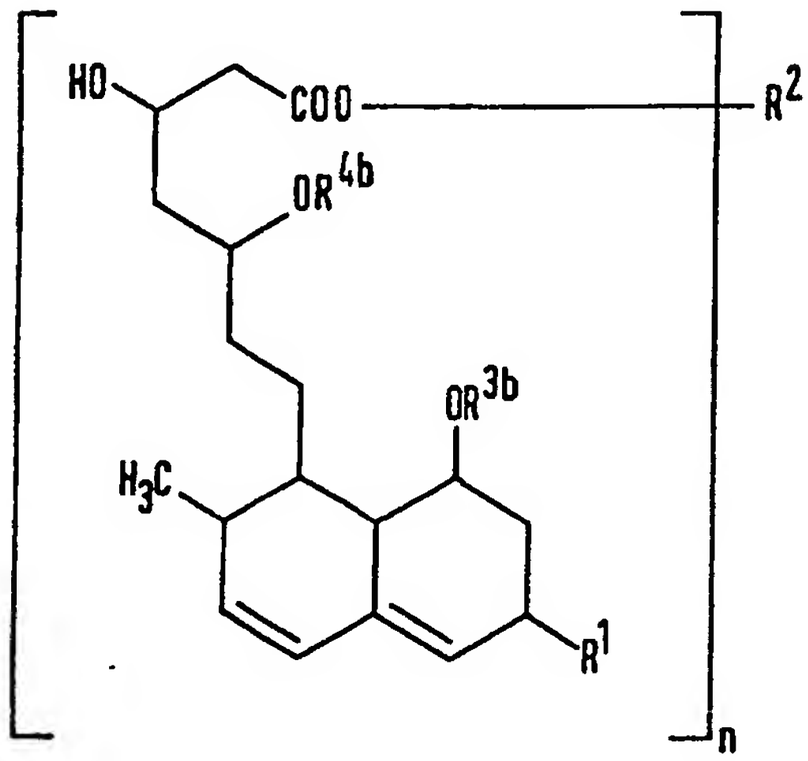
(XII)

(wherein R^1, R^2 and n are as defined above and R^{3c}, R^{4c} and R^{5c} are the same or different and each represents a hydrogen atom or an acyl group provided that at least one of R^{3c}, R^{4c} and R^{5c} represents a hydrogen atom) is acylated.

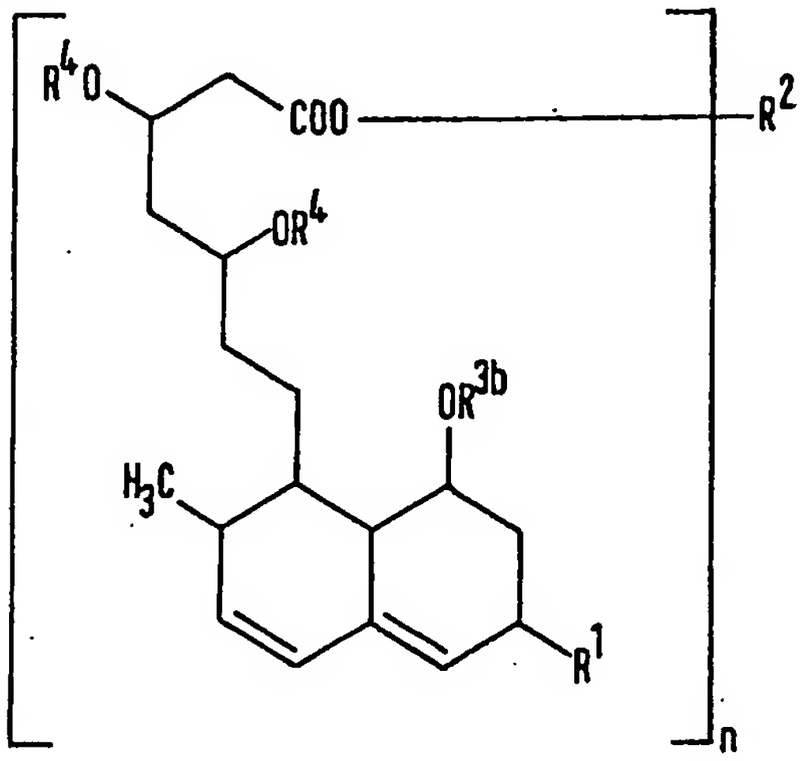
50. A process for preparing one or more compounds of formulae (XIII), (XIV) and (XV):



(XIII)



(XIV)



(XV)

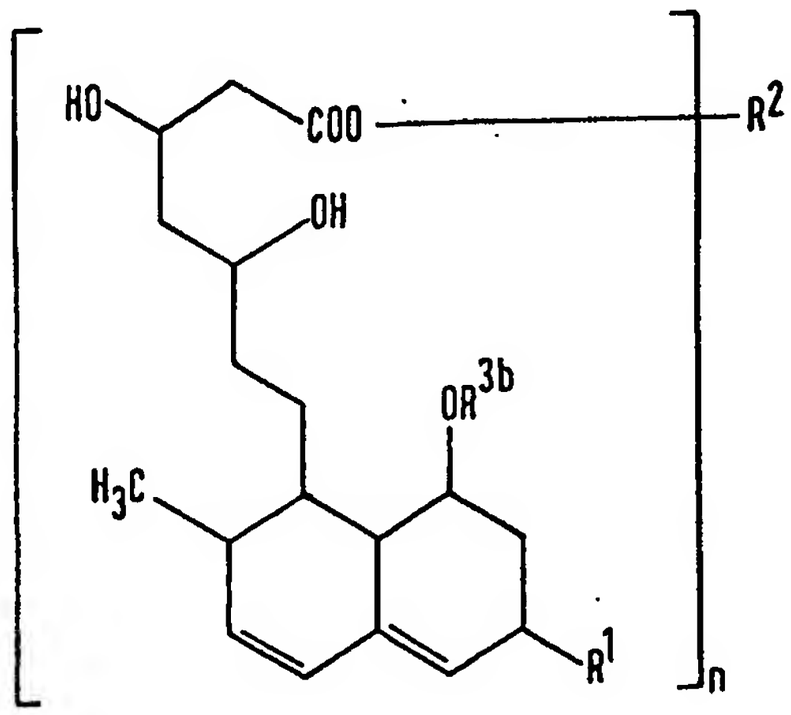
(wherein:

R^1, R^2, R^4 and *n* are as defined in Claim 1;

R^{3b} represents an acyl group; and

R^{4b} represents an acyl group),

in which a compound of formula (XVI):



(XVI)

(wherein R^1, R^2, R^{3b} and *n* are as defined above) is acylated to produce compounds of said formulae (XIII), (XIV) or (XV) and they are isolated from the reaction mixture.

51. A process as claimed in Claim 50, in which, in said compound (XVI):

R^1 represents a hydrogen atom or a methyl group;

R^2 represents an alkali metal atom, a C_1—C_4 alkyl group, a benzyl group or a phenacyl group; and

R^{3b} represents a C_2—C_6 alkanoyl group or a C_3—C_6 alkenoyl group,

said acylation is effected with a C_2—C_6 alkanoic acid, benzoic acid or a reactive derivative thereof, and there is produced said compounds (XIII) and/or (XIV) in which R^{4b} represents an alkanoyl group or a benzoyl group.

52. A process as claimed in Claim 50, in which said acylation is effected with a reactive derivative of a carboxylic or sulphonic acid.

53. A process as claimed in Claim 52, in which said acylation is effected with an acid halide, an acid anhydride or a mixed anhydride of a carboxylic or sulphonic acid.

54. A process for preparing compounds of formula (I), as defined in Claim 1, substantially as hereinbefore described with reference to any one of the foregoing Examples.

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